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NODULAR FORMS OF TUBAL DISEASE.

BY EMIL RIES, M. D., PROFESSOR OF GYNECOLOGY, POST-GRADUATE MEDICAL SCHOOL, CHICAGO.

PLATE XXXII.

In 1887 Chiari (1)* described nodular enlargements of the Fallopian tube which he had found in seven cases out of 760 post-mortem examinations. He designated them histologically as circumscribed hypertrophies and hyperplasias of the muscular wall of the tube with cysts invested with columnar epithelium. The latter he regarded as protrusions of the tubal epithelium following inflammation of the tubal mucous membrane. The cysts were generally filled with serous fluid, in one case with pus. The tubal canal could always be followed up between them. The cysts were surrounded by a very thin layer of connective tissue, resembling in every respect that of the mucous membrane of the tube. In his opinion the circumscribed muscular hyperplasias and hypertrophies are probably the result of the irritation produced by the cystic cavities, which in their turn are caused by inflammation of the tubal mucous membrane. The cysts were never found in the interstitial part of the tube, but were observed occasionally in all other portions of it. In one case it could be proved that the cysts had originated in protrusions of the tubal mucous mem-

* References to literature are at the end of this article.

brane. Chiari regarded these cases as practically identical with Martin's (2) cases of salpingitis follicularis.

In 1888 Schauta (3) added some new cases and gave a sketch of the clinical symptoms appertaining to this salpingitis isthmica nodosa, as he calls it. He has since become fully convinced that this anatomical condition and the consequent clinical symptoms are a result of gonorrhœal infection of the tubes (4).

I shall discuss briefly Schauta's clinical description. The symptoms which he ascribes to the salpingitis isthmica nodosa are subjective and objective. The subjective symptoms, according to him, are identical with those of salpingitis in general, colicky pains recurring principally at the time of menstruation being the most important. These symptoms, however, are not at all characteristic. They occur in tubal diseases of very diverse origin and anatomical condition. The objective symptom, the nodular enlargement of the tube at its starting point from the horn of the uterus is, according to Schauta, sufficient to warrant a diagnosis of salpingitis isthmica nodosa, but Schauta himself comes to the conclusion that the structure of these nodules varies to some extent (3).

The progressive interest in tubal pathology, which has been bred and fostered by the rapid and successful development of tubal surgery, obliges and enables us to re-examine and, where necessary, to reconstruct the older theories. There are still many unsolved problems in the pathology of the tube, and some recent researches seem to open up unexpected vistas in the mysterious regions of pathological cell life and developmental processes. The salpingitis isthmica nodosa is not the least interesting of the pathological conditions of the tube, and a research into its pathogenesis affords abundant opportunities for speculation, from indulging in which I shall refrain as much as possible.

The minute structure of the salpingitis isthmica nodosa will first occupy us, and the question to be answered here is contained in the one sentence: Is the nodular enlargement of the tube always combined with the structural conditions described by Chiari and Schauta?

For some of the specimens which I examined I am indebted to the kindness of Dr. Watkins of Chicago; the rest were removed by Prof.

W. A. Freund or myself at Strassburg. In order to obtain reliable results in these cases it is indispensable to examine series of sections, which I always did, cutting mainly in the sagittal direction, so as to obtain transverse sections of the tube. Some of the specimens were also cut in the frontal direction, which affords special opportunities for the study of the interstitial part of the tube and of some conditions of the tubal wall.

Case I. Miss S. Uterus and both tubes preserved in alcohol.

The body of the uterus is partly covered with membranous adhesions both on its anterior and posterior surfaces. The point where the right tube branches out from the body of the uterus is marked by a nodular enlargement, the size of a hazel-nut. On a sagittal section through this nodule two small grooves, each the size of a pin-head, are discovered which are filled with a pultaceous mass. The walls of these grooves are not smooth, but irregular. The cavity of the tube, from which they are about as far distant as from the peritoneum, follows a pretty straight course between these grooves. The rest of the tube is of normal size and is not tortuous. The left tube is enlarged to double its normal size; the cavity shows a very tortuous course and the walls are thickened. The abdominal portion of the tube contains a nodular enlargement, the size of a filbert. On longitudinal section through this part of the tube the enlargement appears to be caused by a small cyst the size of a pea, which is imbedded in the wall. The contents of this cyst have escaped and cannot be examined. The ovaries show nothing abnormal. The tubes and parts of the ovaries are covered with membranous adhesions.

The *nodule* at the *right horn* of the uterus was excised and a series of sections was made through it. On examining a section through the middle part of the nodule the following conditions are observed (Plate XXXII, Fig. 1): The thickening of the tube is not due to a dilatation of its cavity, which together with its mucous membrane shows the appearances which normally characterize this particular part of the tube. The folds of the mucous membrane are low and few in number; the epithelium is a little lower than usual, but is well preserved over the entire mucosa. The connective tissue of the folds is rather poor in cells and its blood- and lymph-vessels are narrow and empty. There are but slight traces of a previous inflammatory condition of the mucous membrane, signs of which, however, may be found in a certain degree of flattening of the folds of the mucosa.

The enlargement of the tube is not explained by an examination of its

mucous membrane, but a look at the muscular and connective tissue of the tube accounts for it. We see here, first, a considerable thickening of the muscular layers; and secondly, accumulations of round cells and epithelial cysts imbedded in the connective tissue between the muscle bundles.

The muscular layers which are thickened are almost exclusively the circular and not the longitudinal coats. I have not been able to confirm Chiari's observations of hypertrophy of the muscle fibres, but have only found hyperplasia, that is to say, the number of the muscle fibres exceeds the normal, but the shape and size of the fibres are unchanged. The hyperplasia of the muscular tissue is so great that the muscular wall attains in places to five times the normal thickness.

While the bulk of the nodule is composed of the thickened muscular tissue, another factor cannot be overlooked, viz. the accumulations of round cells and the cysts. Outside the muscular layer encircling the mucous membrane and reaching out to the longitudinal muscular layer, a mass of round cells is seen corresponding to the pultaceous mass filling the small grooves described above. The single cells composing this mass are of the typical round type and lie closely together. In some places a few connective-tissue fibres are seen between them, in others small hæmorrhages. In the centre the mass of round cells has broken down in two places and two cavities with irregular walls have been formed. The cells surrounding them show the presence of necrosis by an imperfect degree of staining. The accumulations of round cells have no sharp outlines, but spread irregularly between the muscle and connective-tissue bundles in the neighborhood.

Imbedded in these masses of round cells we find epithelial masses of various sizes and shapes. In some places the latter form almost round cysts, in others the outline is very irregular. Several of these epithelial masses do not form continuous epithelial lines, the latter being interrupted, as if broken up and destroyed by the masses of round cells. The cells of these epithelial masses are mainly of the columnar epithelial type and are generally of the same size and height as those of the tubal mucous membrane. In some of the round cysts the epithelial cells are rather more cuboidal than cylindrical, a result of the pressure exercised by the contents of the cyst. The contents consist of detached epithelial cells, some round cells and occasional hyaline drops. The epithelial masses sometimes project into the cavity of the cysts, forming papillary elevations. In other cases there is no regularity in the arrangement of the epithelial cells, especially where the accumulations of round cells have entered into and separated the epithelial masses. Cilia are nowhere to be found on the epithelial cells.

The epithelial masses imbedded in the accumulations of round cells are not the only ones to be found in this specimen. Numerous epithelial cysts, round or oblong in shape, some with papillary elevations of the epithelial cells, are met with between the cavity of the tube and the mass of round cells. They are invariably surrounded by a thin layer of connective tissue resembling that of the mucous membrane of the tube. In one place a ramifying cavity invested with columnar epithelium and surrounded by a layer of connective tissue is seen, of which I shall have to treat later.

The peritoneum shows in some places slight thickening and new formation of connective tissue, but nowhere in a very high degree.

If we start from this description of one section and add to it the observations to be gathered from the series of sections, we are able to say a little more about the extent and course of the various changes described above.

We find the hyperplasia of the muscular tissue throughout the entire nodule. The accumulation of round cells is observed to follow an oblique course from the mucous membrane of the tube towards the peritoneum. It forms at one place a semicircle around the mucous membrane of the tube, then is seen midway between the mucosa and the peritoneum, and at last approaches the peritoneum, which it reaches at a point where some hæmorrhagic infiltration of the tubal connective tissue prevails. With this mass of round cells the epithelial masses, described above, proceed from the cavity towards the peritoneum, some imbedded in the masses of round cells themselves, some at a short distance from them. The ramifying cavity with epithelial lining, described above, is with the aid of the series recognized as belonging to the tubal cavity itself. A sharp curve of the tubal cavity causes it to appear twice in the same section.

After the examination of the nodule I excised part of the *uterine horn*, of which again a series of sections was made. In this series the mucous membrane of the so-called interstitial portion of the tube shows a normal appearance, and we have a very narrow cavity lined with an epithelium lower than that of the rest of the tube and approaching in size and shape to the epithelium of the uterine body. The folds of the mucous membrane are few (two to four) and very low. Besides this there are no epithelial elements to be seen in the sections. The sections contain accumulations of round cells in two different places, one near the anterior, the other near the posterior surfaces of the horn of the uterus. Again these accumulations are very dense and again they contain central cavities where the cells have perished, leaving a hollow with an irregular outline.

No giant cells are found, and no evidences that these small abscesses, as we must term them, are of a tuberculous nature. The peritoneal covering of the uterus shows some thickening caused by membranous adhesions, but otherwise neither here nor in other parts of the peritoneal covering of the uterus can pathological changes be discovered.

The rest of the *body of the uterus* and the *cervix* were then examined. The body shows some pathological changes. The muscular and connective tissues in some places are infiltrated with round-cell accumulations which have occasionally become so marked that they must be termed abscesses. The cervix is free from round-cell infiltrations; the mucous membrane shows no signs of infiltration or hypertrophy. I paid special attention—from reasons to be explained later—to the search for remnants of the Wolffian duct in the walls of the uterus, but could not discover any.

Finally that part of the *left tube* was examined which contains the nodular enlargement caused by the cyst of the tubal wall. The cyst is lined with a low cylindrical epithelium which in some places forms secondary cysts, the cavities of which remain only as narrow clefts in consequence of the pressure of the contents of the main cyst. These secondary cysts communicate with the larger cyst through wide openings. The cyst is surrounded by a thin layer of connective tissue. No communication between the cyst and the cavity of the tube is to be traced out. The mucous membrane of the left tube shows traces of old inflammation, atrophic folds of the mucous membrane, and a dense fibrous condition of the connective tissue of the mucosa. The contents of the cyst had escaped. There is no hypertrophy of the muscular tissue of the tube.

We have in the foregoing specimen a nodular condition of both tubes. But while the findings in one nodule tally exactly with those described by Chiari, the other owes its origin to a vastly different structure. On the right side we find the tube enlarged in consequence of hyperplasia of the muscular tissue and of the existence of an inflammatory new formation, an abscess, and a number of epithelial structures, cystic and otherwise. The same inflammatory condition prevails in the right uterine horn and other parts of the body of the uterus. On the left side the enlargement has nothing to do with changes in the muscular tissue, hyperplastic or inflammatory, but is due to the existence of a cyst in the wall of the tube.

Case II. Mrs. S—t. Both tubes.

The fimbriated ends of both tubes are open. The tubes are straight, not tortuous. The left shows a nodular enlargement the size of a cherry at the tubal horn of the uterus. Each tube shows, in addition, one nodular enlargement in the neighborhood of the abdominal end.

The nodules situated near the abdominal end of either tube show the same gross condition on vertical sections. The muscular coat is very thin (0.5–1.5 mm.) and the rest of the section consists of the enormously enlarged mucous membrane of the tube. The nodule of the left uterine horn shows a different appearance on section. It is impossible to outline the muscular coat, and the central parts appear homogeneous.

On microscopical examination of serial sections through these nodules the following changes are observed:

a. Nodule of left uterine horn.—The cavity of the tube is narrow. It is lined with the normal cylindrical epithelium and presents two or three short folds. The mucous membrane is surrounded by the normal circular muscular layer. The cavity of the tube lies excentrically near the anterior and superior surface of the tube. The longitudinal muscular layers of the tube are very thin. Between the longitudinal and the circular layers of muscle fibres the entire space is filled with a dense accumulation of round cells, with a few connective tissue fibres and some small hæmorrhages, except for a central irregular cavity, which is surrounded by necrotic masses of round cells and a small area of cells containing blood pigment. The infiltration with round cells penetrates between the longitudinal muscular layer, but does not reach the peritoneum. No epithelial formations. No giant cells. No signs of tuberculosis.

The accumulation of round cells followed up through the series of sections proves to be a body of oval shape without direct communication with the cavity of the tube, the peritoneal surface or even the broad ligament. The peritoneal covering is normal.

The specimen would correctly be termed abscess of the tubal wall or salpingitis abscedens.

b. Nodules near abdominal ends of both tubes.—Both nodules are of the same structure. The muscular coats are very thin, representing about one-tenth of the diameter of the tube, while the bulk consists of mucous membrane. The latter presents very hyperplastic, markedly ramifying folds. A few of them are high and thin; others are thin at the bases, have a stem with ramifying branches and then swell up into a thick mass, from which new folds branch out. In some places two folds starting from different points form an arcade-like arch. The whole mass of folds forms the walls of a confused labyrinth of clefts and chinks,

the rest of the tubal cavity. In a few places the cavity is a little larger and is full of round cells, masses of red blood corpuscles and some detached epithelial cells. The epithelium covering the folds varies from the cuboidal to the high cylindrical type. In some places vacuoles are seen in a group of columnar epithelial cells. Most of these vacuoles contain one or several round cells; they vary somewhat in size; some of them are connected with neighboring vacuoles; they are generally surrounded by a line of flattened epithelial cells. The connective tissue of the mucous membrane presents a very pronounced infiltration with round cells, between which, in places, none of the connective tissue can be recognized. The blood-vessels are not very numerous and are choked with red corpuscles.

The circular and longitudinal muscle layers are both very thin; in some places there is only a mere indication of them. Between them there are copious infiltrations with round cells and some small hæmorrhages.

The peritoneal covering shows some very remarkable changes, of which I shall speak later on in detail.

We have in this case a nodular enlargement of the isthmic part of the tube, the histological condition of which differs from that described by Chiari in the absence of both muscular hyperplasia and epithelial formations. Schauta himself mentions (3) the occurrence of such cases where the outward appearance pointed to the existence of a salpingitis isthmica nodosa, but the microscopic investigation showed only accumulations of round cells without any epithelial formations. The nodules of the abdominal portions of both tubes show still less agreement with Chiari's and Schauta's description. They present a picture commonly observed in salpingitis catarrhalis with considerable swelling of the folds of the mucous membrane.

Schauta (3) refers to Hegar's report (5) of cases of tuberculosis of the tubes which presented the same nodular condition that gave origin to the term salpingitis nodosa.

Case III. In sections from a tube which showed a nodular enlargement in its isthmic part, I was able to find clear evidence of the tubercular nature of the disease. The mucous membrane, as well as the wall and the peritoneal covering of the tube, contain numerous tubercles with beautiful giant cells. Of epithelial cysts in the wall

of the tube outside the mucous membrane, there are no traces to be found.

Hegar found (5), on two occasions, nodules at the starting point of the tube which he had felt distinctly before the operations and which he had been able to satisfy himself were caused by a hypertrophy of the wall resulting from the presence of a pathological substance. After cutting through this part of the tube during the operation cheesy tubercular masses resembling long thin worms could be squeezed out at several points of the incision. He concluded, therefore, that all of them did not issue from the stenosed cavity, but that some came from lymphatic vessels. The same observation in the case of tubercular nodules in this part of the tube has been made by other observers—Gusserow (6), Courty (7), Reynaud (8), Mosler (9). Nodules occur in all parts of tubercular tubes; they are often multiple, so that the tube looks like a string of beads. The nodules are soft or hard, according to the degree of hypertrophy of the wall, the tension of the contents and the more or less advanced liquefaction of the tuberculous products.

In addition to the condition described by Chiari, from observation of our cases we have become acquainted with several other structural changes in the tube which may give rise to nodular enlargement. Among these were abscesses and cysts of the tubal wall, tuberculosis of the tube and catarrhal salpingitis. But, even now, this interesting subject is not exhausted. On further examination of specimens from cases of tubal disease, we come across a number of abnormal structures which must be compared with and differentiated from the condition first discussed. We shall meet in some cases with the same elements which make up the salpingitis isthmica nodosa, but existing in a great variety of combinations. We see epithelial formations in the tubal wall without inflammation, without hypertrophy of the muscles and with or without nodular enlargement. We find, furthermore, muscular hypertrophy and epithelial formations without inflammation and with or without the formation of nodules; lastly, we find muscular hypertrophy and inflammation without epithelial formations and without formation of nodules.

The cyst found in Case I, and which was described above, is an epithelial formation in the wall of the tube. It is not accompanied by hypertrophy of the muscular tissue. It forms a nodule. It has nothing to do with inflammation, so far as I can determine. A number of cysts from various parts of tubes showed structures identical with this one, but in no case could I discover muscular hypertrophy or traces of inflammation. If sufficiently large, they cause a nodular enlargement of the tube. Bimanual palpation would not reveal any difference between this condition and a salpingitis isthmica nodosa. Anatomically such a cyst may by secondary infection of its wall and contents undergo such changes that the condition may come to show a great similarity with that of a salpingitis isthmica nodosa, though originally the difference is sharply pronounced.

So far I have described only cases which on bimanual palpation or gross anatomical examination might be called instances of salpingitis isthmica nodosa; I have at the same time proved that a nodular condition of the isthmic portion of an inflamed tube is not necessarily caused by Schauta's salpingitis isthmica nodosa. Consequently it must be confessed that the clinician has no reliable means of diagnosing the condition previous to operation and microscopic examination.

In considering the origin of the detached epithelial masses, not only the conditions described above and which are actually characterized by nodular enlargement of the tube will have to be taken into account, but a number of others in which epithelial masses are present in the wall of the tube.

Chiari's theory of the origin of the detached epithelial masses from the epithelium of the tubal mucous membrane is the most likely to be accepted as correct wherever a direct connection between the epithelium of the mucous membrane and that in the tubal wall within the muscular layers is demonstrable. In some places where a direct epithelial connection cannot be observed, the layers of infiltrated connective tissue which accompany and here and there break up the epithelial masses form, according to Chiari's opinion, the connecting link and give evidence of the route which the epithelium has taken. But in view of the fact that this explanation, although perhaps the most

satisfactory yet advanced, has never been absolutely proven, it is well worth while to consider some other possibilities. Experiments on this subject are out of the question, a fact much to be regretted, as they would furnish the best means of elucidating the causal connection. Fortunately nature has stepped in to some extent and has produced a number of different combinations of pathological conditions resembling more or less the peculiar form of salpingitis which we are discussing.

Epithelial formations in the wall of the tube occur under various conditions, some of which must be considered as congenital, others as acquired.

Among the abnormalities in development of the tube, the formation of accessory ostia and their equivalent, the accessory tube, has recently attracted renewed attention—Kossmann (10), Nagel (11). It has been found that these pedunculated accessory and rudimentary tubes occur more frequently than has been generally believed (according to Kossmann (10) in four to ten per cent of all cases). They contain sometimes a central cavity which, according to Kossmann, never communicates with the lumen of the tube, but opens in many cases into the abdominal cavity, while in others it is closed at both ends. These accessory tubes start from the main tube or from the broad ligament.

Case IV has provided me with a specimen in which two very well-developed accessory tubes start from the broad ligament. The end of one forms a cyst the size of a pea, while the other terminates in a number of fimbriae, just as in the normal tube. On microscopic examination the accessory tube with the fimbriae was found to contain no cavity. Its fimbriae formed dendritic growths invested with the same high columnar epithelium which lines those of the normal tube. The pedicle consisted of muscular and fatty tissue with comparatively large blood-vessels, but contained no epithelial formations.

The attention of anatomists has been directed exclusively to those accessory tubes which possess more or less pronounced pedicles. No attempt has been made to utilize these formations in the explanation of two other conditions which I think may justly be derived from the

same source, the cysts of the tubal wall and the accessory tubal cavities or diverticula of the tube. Of the cysts, I have already described one specimen (Case I); of accessory tubal cavities, there are only a few instances mentioned in the literature, and I have myself observed only two cases, which I discovered accidentally when examining microscopically tubes which showed no outward sign of such accessory cavities.

Case V. The first is a case of dermoid cyst of the ovary which was removed with the tube. The tube presents no gross appearances of disease of any kind and was removed merely because it formed the pedicle of the tumor. On examining the tube microscopically I found the mucous membrane normal and its folds well developed; there were no pathological changes in the substance of the wall. Unexpectedly I came upon epithelial formations in the wall lined with cylindrical epithelium situated near the peritoneal coat of the upper border of the tube outside the circular muscular layer and surrounded by connective tissue and some of the longitudinal muscular layers of the wall. I had made a series of sections and was therefore enabled to follow up the epithelial formations throughout their entire length. I found that they formed a duct with several ramifications, so that in some sections two, or even three, accessory cavities were seen; in other sections the cavity was single and lined with a circle of columnar epithelium. The accessory cavity did not communicate with either the mucous or the serous surface of the tube. The epithelium forming this duct possessed no muscular wall of its own, but was surrounded by connective tissue.

Case VI, a. The second case of this kind was observed in a tube which Dr. Rumpf had removed together with the myomatous uterus by abdominal hysterectomy. The tube appears thickened and the mucous membrane presents a honey-comb appearance. What interests us here is the following observation: In the wall of the tube outside the longitudinal muscular layers it is possible to demonstrate an irregular cavity lined with columnar epithelium and presenting a few short ramifications. The epithelium resembles precisely that of a normal tube. In this case also the epithelial formation has no mus-

cular wall of its own, but is surrounded by connective tissue. The accessory cavity does not communicate with either the tubal cavity or the peritoneal surface. The same tube presents another unusual arrangement of epithelial formations, of which I shall speak more in detail later (see Case VI, b, p. 374).

These two instances of accessory tubal cavities clearly belong to the same class as the case of Landau and Rheinstein (12), in which they described a diverticulum of the tube. The only difference, and one which I do not consider essential, is that in their case the accessory cavity must have communicated with either the peritoneal surface or the main cavity of the tube, although such a statement is not made in their paper. It is proven, however, by the fact that the diverticulum had become the seat of a tubal pregnancy, and that in consequence of rupture of the sac the patient had succumbed. The tube of the other side also contained a similar diverticulum. It is not necessary to dwell upon the importance of such accessory cavities of the tube in regard to the causation of extrauterine gestation. Rokitansky (13) enumerates "hernial protrusions of the mucous membrane of the tube through the muscular layer" as one of the possible causes of tubal pregnancy, and this view has been adopted in all subsequent works on this question, mainly, as it would seem, on Rokitansky's authority, and not in consequence of very frequent observations of this kind. It is evident that there is no way out for an ovum which has once wandered into such an accessory cavity. It is noteworthy that very little is said about this malformation in the literature upon tubal diseases, but that a work dealing with extrauterine pregnancy by Werth (14) contains two more cases of accessory cavities with an epithelial lining situated in the tubal wall.

Werth's cases differ from those described above by the fact that in the former a great number of accessory cavities were found in the tubal wall. Werth himself regards these additional cavities as caused by active growth of the epithelium of the tubal mucous membrane in consequence of the irritation due to the existing pregnancy. He mentions, however, Martin's report (2) of cases of follicular salpingitis where the accessory cavities in the wall of the tube were the result, not of pregnancy, but of inflammatory irritation.

The follicular salpingitis of Martin we shall consider more closely later on. At present we shall deal with the origin of the accessory cavities and their relationship to the accessory tubes. It is clear that, as in the case of other tubular organs, a double, threefold, or even more complex, Mueller's duct can originate in the course of embryonic development. It is a generally accepted theory that the well-known pedunculated accessory tube or parasalpinx, as Kossmann (10) terms it, originates in this way. Now there is no fact in embryology which forces us to assume that such an additional tube must invariably be pedunculated. It may just as well grow within as outside the wall of the tube. If it has an opening at both ends it forms an accessory ostium through which a probe can be passed down into the cavity of the tube. If the abdominal end is closed and the termination on the mucous membrane is open, the parasalpinx forms a diverticulum communicating with the cavity of the tube. Kossmann's statement that the parasalpinx never communicates with the lumen of the tube is not opposed to this view, since he would limit its application to the pedunculated parasalpinx and lays down the fundamental principle that the accessory ostium and the accessory tube originate in developmental processes which are the same and differ only in degree. The positive observations of pregnancy in diverticula are rather in favor of the theory given by me.

If both ends of the parasalpinx are occluded, it forms an accessory cavity in the wall of the tube, an "intraparietal parasalpinx," as described in Cases V and VI. If exudation of fluid takes place into this accessory cavity, the formation of a cyst in the wall, an "intraparietal hydroparasalpinx" will be the consequence. If an inflammation spreads from the mucous or serous surface of the tube into such a parasalpinx, which is partly or totally occluded, the inflammatory round-cell infiltration, which may even break up or to some extent destroy the epithelial formations, must evidently produce a condition which it will be impossible to differentiate from Schauta's salpingitis isthmica nodosa. It will be very difficult or even impossible to tell whether the epithelial formations were primarily in the tubal wall and participated in a secondary inflammation or whether the inflam-

mation preceded and caused the epithelial masses of the mucous membrane to later invade the wall of the tube.

There are, however, some few points which may prove of value in attempting to arrive at a differential diagnosis between these two conditions. Accessory intraparietal tubes are generally few in number (I have not observed more than one in the same tube), and accordingly accessory cavities within the wall are also few. Furthermore, they generally show only few and insignificant ramifications. Of epithelial growths resulting from inflammatory irritation, there may be many and these most irregular in shape. A non-inflamed accessory tube is surrounded by connective tissue, while the epithelial growths caused by inflammation of the mucous membrane are accompanied by connective tissue and masses of round-cells. Secondary inflammation of an intraparietal parasalpinx will of course wipe out this difference.

The parasalpinx is only one of the malformations which are of significance in regard to the subject under discussion. The parasalpinx is a product of Mueller's duct, but the Wolffian duct may also play no unimportant part in the causation of epithelial formations in the tubal wall.

The importance of the Wolffian body in this regard has been ignored until very recently. A number of authors had described myomatous tumors of the uterus which contained cysts invested with ciliated cylindrical epithelium (Rokitansky (15), Babes (16), Diesterweg (17), Hauser (18), Ruge (19), Ricker (20), and others). But it remained for Breus (21) and Recklinghausen (22) to prove their origin to be in the Wolffian body or duct. Recklinghausen also was the first who gave a thorough description of such tumors in the Fallopian tubes. These myomata, whether they are situated in the uterus or in the tube, or even outside and at a distance from the uterus (Breus and Recklinghausen), have one characteristic in common, namely, that they contain glandular elements (hence the name "adenomyoma") or cysts invested with ciliated cylindrical epithelium imbedded in a thin layer of connective tissue which contains numerous round cells ("cyst-adenoma"). Another frequent but not invariable finding is that these myomata have no capsule separating them from the mus-

cular tissue of the uterus, but their muscle fibres are so intimately interlaced with those of the surrounding muscle tissue that it is impossible to find a distinct border line between the tumor and the healthy tissue. All other signs, such as location of the tumor, shape of the uterus containing such tumors, or the general appearance and development of the patients (Freund (22)), are less reliable.

The theory evolved by Recklinghausen is briefly as follows: The Wolffian body, which in the normal development of the human female usually becomes entirely atrophied, in a comparatively large number of cases is found to be well preserved and located in the wall of the uterus or the tube. Wherever such remnants of the Wolffian body exist, tumors can develop which contain the elements of it, ciliated cylindrical epithelium and connective tissue.

It is due to Recklinghausen's classic and exhaustive work that we have become acquainted with the peculiarities of the structure of these tumors. These characteristics remove them from the histioid variety and show them plainly to belong among those extremely interesting tumors which are termed organoid, because they imitate and reproduce not only the histological components, but the entire structure and architecture of the organ from which they have sprung. Recklinghausen has shown that these adenomyomata contain a system of terminal bulbs, secretory and collecting channels linked together by loops, cistern-like cavities or ampullæ, terminating finally in a main channel—in short, an epithelial system, the parts and combination of which closely correspond to those observed in the Wolffian organ during embryonic life. The similarity is further emphasized by the formation of pseudo-glomeruli and by the existence of pigmented cells. Other minor points of similarity I omit here because their discussion would lead us too far. What has been said is sufficient to establish the theory of the derivation of these adenomyomata from the Wolffian body and to establish it with as much certainty as can be gained from the observation of morphological conditions.

It is noteworthy that the growths which afforded Recklinghausen the opportunity of observing this close resemblance were large tumors of the uterus, while the smaller tumors of the tubes showed a less

pronounced resemblance between the arrangement of their epithelial ducts and that of the ducts of the Wolffian body.

Satisfactory proof of their derivation from the Wolffian body is much harder to establish in the case of these tubal tumors than in the uterine tumors, and the facts at hand would probably not be considered conclusive if the same theory could not be proven so beautifully in the cases of the uterine adenomyomata.

It is true that it seems impossible to contest this theory for the cases so well described by Recklinghausen. But now a new question arises. Is this origin the invariable rule? It is highly interesting to read how tenaciously, for some 220 pages, Recklinghausen defends his theory of their origin in the Wolffian body—in some cases against serious objections which he by no means refuses to recognize—and how at last in a postscript he has to acknowledge that just before publishing his book he has encountered a case which does not allow of any other explanation than that of the origin of the adenomyoma in the uterine mucous membrane and not in the Wolffian body.

Recklinghausen claims that Chiari's cases (1) of what Schauta (3) termed "salpingitis isthmica nodosa" and Martin's (2) and Orthmann's (25) cases of "salpingitis pseudo-follicularis" were identical with his instances of adenomyoma and that these growths must all be derived from the Wolffian body and not, as Chiari and Martin assume, from the tubal epithelium. I was glad to see this claim of Recklinghausen's, since it proves the great difficulty of discerning between these cases, a difficulty which I have experienced myself but which I do not believe can be simply put aside by declaring the origin of all of these cases to be identical.

Some objections against the theory of Recklinghausen can be upheld in view of what has been said above in the description of Chiari's cases and my Case I. The question of inflammation has received almost no consideration in Recklinghausen's book. He does not mention the finding of pus in one of the small cystic cavities of the tube, which it is true Chiari observed only in one out of seven cases. But I believe, and my Case I confirms this opinion, that the question of inflammation as a cause of such tubal adenomatous growths deserves a

great deal of attention on account of its practical and clinical importance, as well as its theoretical interest. At least we must consider the possibility of inflammation attacking a tube already abnormal in consequence of previous inflammation or congenital malformation, a complication which I have pointed out repeatedly and which Recklinghausen seems inclined to admit. My Case I, I believe to be a case of adenomyoma tubæ Wolffianum with secondary inflammation.

Recklinghausen is decidedly opposed to the theory of the origin of the glandular elements of the adenomyomata from the epithelium of the tube, one of his principal reasons being that, as the tube contains no glands, its epithelium cannot give rise to the formation of glands in the neighborhood of the tubal cavity. Recklinghausen himself observed an epithelial cyst located outside the circular muscular layer and connected with the epithelium of the tubal cavity by a long, thin duct. But the explanation he gives is that the cyst which originated in the Wolffian body has broken into the mucosa of the tube, not that the epithelium of the mucosa has invaded the surrounding tissue. I believe that one of my observations (Case IX) will enable me to show that this explanation does not hold good in all cases, and that in tubal as well as in uterine adenomyomata the origin of the epithelium may be traced in certain cases to the mucosa of the organ and not invariably to the Wolffian body.

I possess specimens of six tubal nodules which have to be termed adenomyomata of the tube.

Case VII. Mrs. N—n. Both tubes.

One tube has a thickened nodular uterine end, the fimbriae are open. The tube is very tortuous and presents three nodular enlargements of the isthmic part, which are made more evident by strangulation of the rest of the tube. Microscopic examination reveals the thickening to be caused by an abnormal amount of muscular tissue and by an unusual amount and distribution of epithelium.

The cavity of this tube is a narrow slit made irregular by two or three elevations of the mucous membrane. The epithelium is normal in size and arrangement. The connective tissue of the mucous membrane is free from round cells and rather dense and fibrous. The mucous membrane is surrounded by a strong circular muscular layer. Between the

latter and the well-developed longitudinal layer a new layer is interposed, which in some specimens takes up about two-thirds of the diameter of the tube. This layer contains epithelial formations, muscular and connective tissue and numerous large blood-vessels. In some sections the epithelial formations are found all around the cavity, in others, more especially between the cavity and the insertion of the broad ligament on the tube. The relative arrangement is the following: The epithelium forms more or less regular circles or gland-like ducts; it is elevated in some places after the manner of papillary growths. Of the gland-like ducts, two to four sometimes lie in the same direction and very near together. The epithelial cells of these formations are columnar, the nucleus occupying about the middle of the cell. Some of them present very well defined cilia. In the dilated or cystic formations the epithelium is frequently cuboidal rather than cylindrical. The cyst-like dilatations of the ducts contain numerous cells which resemble the epithelial cells on the walls of the cyst and do not stain well. They are probably detached and degenerated epithelial cells. The epithelial lines are surrounded by a layer of connective tissue which is sometimes very thin, sometimes well pronounced. Outside the connective tissue comes a thick layer of muscle cells which are arranged parallel to the epithelial lines. so that they appear circular around the cysts and oblong or loop-like around the gland-like ducts.

Each epithelial line with its sheath of connective and muscular tissue forms a system of its own, which is separated from the neighboring systems and from the muscular layers of the tube proper by a stratum of loose connective tissue. The whole picture resembles somewhat that of the parovarian tubules just outside the tube in the broad ligament, but the muscular layers are much more pronounced here than is usual in the parovarian tubules.

There is no connection between these epithelial systems and the cavity of the tube. Hæmorrhage or pigmentation is nowhere to be seen. The same is true with regard to round-cell infiltration. There are no signs whatever of inflammation.

The other tube presents a thickening, measuring 3 cm. in length and 2 cm. in thickness, in which the tube disappears. On microscopical examination of one-half of the tumor the cavity of the tube is found to be obliterated at the extremity of the tumor, while in the centre it is well preserved and provided with numerous and slightly ramifying folds of mucous membrane. The epithelium of the folds of mucosa is of the normal columnar type in the centre, while towards the thin end of the tumor it is perfectly flat or entirely absent. The cavity is gaping in

the centre, but towards the extremity of the tumor appears as a mere capillary cleft, which at last is barely recognizable. The tissue between the epithelium and the circular muscular layer is dense and fibrous, not at all like the normal tissue of the tubal mucous membrane. The circular layer is normal, not thickened.

The tumor is the result of the presence of an increased amount of muscular tissue between the circular and the longitudinal muscular layers and of epithelial formations imbedded in this abnormal muscular tissue. The epithelial formations and their relations to the surrounding tissue are almost the same as in the nodule of the other tube described above. One finding, however, is peculiar to this nodule, namely the occurrence of concretions with concentric strata not perfectly globular but possessing slight wave-like curves in their outlines. These concretions present a hyaline appearance. They are found in the epithelial cysts outside the tubal cavity and are in some cases surrounded by flat epithelium; in others they appear imbedded in the connective tissue itself. Being unwilling to destroy the sections, I could not test the concretions with acids.

It is noteworthy that the epithelial formations are numerous and larger in the centre of the tube where the tubal epithelium is well developed, while at the thin end of the tumor, where the tubal epithelium disappears and the lumen is obliterated, the epithelial formations are absent.

The nodular enlargement of the tubes in this case is caused entirely by the growth in them of the epithelial elements and their sheaths of connective and muscular tissue. Without them the tubes would be of about normal size.

In the light of modern research this case must be regarded as one of adenomyoma of the tube. It is not a simple hypertrophy of the muscular tissue, since the muscular sheaths form separate nodules around each epithelial nest. That the epithelial formations cannot be derived from the epithelium of the tubal cavity is shown by the fact that no connection between them is to be discovered and no traces of any irritative process in the epithelium of the tube proper exist. The only observation which might give rise to doubt upon this point is the coincidence of well developed tubal mucosa with numerous epithelial masses in the wall and of obliteration of the lumen with absence of epithelial masses outside, as described in the nodule of the second

tube. As, however, I was not able to find any direct communication between tubal epithelium and epithelial formations in the wall, it would seem that too much importance must not be attached to this coincidence. The facts are in favor of the theory of a separate origin of these epithelial formations, and this separate origin is to be accounted for by aberrant and non-atrophied parts of the Wolffian body.

Case IX. Mrs. W.

I received from Dr. T. J. Watkins, who performed the operation,* the tube of one side and a disk fifteen millimetres in diameter and six millimetres thick, cut out of the isthmic part of the other tube, the abdominal end of which was open. The second tube was not removed, but united with the uterus by an operation which might be called "metro-salpingo-anastomosis" and of which Dr. Watkins will soon publish a description.

The disk was resected, because at this point the tube showed a distinct tumor. On macroscopic examination the tissue was extremely firm and dense and did not show a distinct lumen of the tube.

Microscopic examination revealed the following condition: The tube contains a distinct cavity with from three to five folds invested with the normal columnar epithelium. The connective tissue of the mucous membrane is dense and fibrous. The circular muscular layer around the mucosa is well pronounced with the exceptions to be described.

The enlargement is caused by an abnormally thick layer of muscle tissue interposed between the circular and longitudinal layers of the tube. This layer contains numerous epithelial formations, some of which show a more or less round or cyst-like appearance, while others are elongated like glands. Many of the ducts are tortuous, others straight but ramifying. Some are surrounded by connective tissue with numerous round cells, others directly by muscular tissue. The muscular tissue forms sheaths around some of the epithelial formations, the fibres closely following the outlines of the ducts or cysts. Other epithelial formations are scattered through the tissue without forming centres of concentrically arranged muscle fibres. Some of the cysts are fairly large and are filled with detached epithelial cells or with hyaline concretions arranged in many concentric layers; others are smaller and contain nothing or only

* Dr. T. J. Watkins' operation consists of the following steps:

1. The nodule of the tube is excised.
2. An incision is made extending into the cavity of the uterus.
3. The tube is inverted into this opening and
4. Fastened with stitches.

a few cells. The epithelium of these formations is columnar throughout the specimen. Cilia could not be observed. The epithelial formations are found in the entire space between the central circular and the external longitudinal muscular layers.

On the short length of tissue of six millimetres a finding which is of the highest interest with regard to the pathogenesis of these epithelial formations was observed in three different places, namely, the observation of open communication between the tubal epithelium proper and the epithelial formations in the wall.

The points of communication show the following condition in transverse sections: The mucous membrane and its epithelium has the same appearance as in the other sections, but the circular muscular layer is interrupted along an extent of about one-tenth of its circumference, and through this opening the epithelium of the tube is seen communicating in several lines with the epithelial masses in the tubal wall. The communication takes place not by a single wide hole, but through a number (three to four) of duct-like channels. At the place where this epithelium interrupts the circular muscular layer, there is no constriction of the epithelial masses. The distance between the two nearest points of the circular muscular layer is about 0.2 mm.; the greatest width of the gap is 0.6 mm. The calibre of the epithelial ducts leading from the tube into the wall is between 40–80 μ in cross section. As I had made a series of sections, each of 15 μ in thickness, I was able to determine how large the opening of these communications is in the diameter vertical to the transverse section. Since this was found to be between 250 and 300 μ, and when we take into consideration the great extent in length of the opening, we cannot properly speak of gland-like ducts, but must regard these openings as deepened folds of the mucosa of the tube, which have penetrated the muscular wall. The epithelial cells of the tubal mucosa proper and of the epithelial formations outside the mucosa proper are absolutely identical in appearance. I have been unable to find any difference whatsoever between them. I mention this point more especially because Recklinghausen reports a similar observation which, however, he explains as an invasion of the Wolffian body into the mucosa for two reasons: first, on account of a slight difference in shape and staining between the cells forming the communication and those of the tubal epithelium proper; and secondly, on account of the narrowness of the communication, which would contra-indicate its being regarded as a diverticulum.

In this connection Recklinghausen lays stress upon the absence of glands in the normal tube, but a communication, like the one I have

described just now, is not really formed by a gland-like duct, but by a real diverticulum, for as such the great width of one diameter of this communication forces us to regard it. Another point of great importance is the repetition of the same observation in three different places in a length of 6 mm. of tube. A perforation of the Wolffian body into Mueller's duct in three different places within 6 mm. is difficult to assume, where the circular muscular layer must have offered an obstacle to the progress of growing epithelium. It is true—and this is a fact which the incomplete literature on the circulatory system of the tubes has not before recorded—that there is one prearranged route, following which growing masses of cells will encounter diminished resistance. I have repeatedly observed small arteries breaking straight through the circular muscular layer of the tube and ramifying in the mucosa of the tube. But in the case described here, I have not been able to find a blood-vessel for the epithelial masses to follow in the course of their penetration of the circular layer from without inward.

With regard to the repeated observation of such communications in a short length of tissue, I must again refer to Recklinghausen's last case mentioned in his postscript, in which the presence of numerous communications between mucosa and epithelial formations in the wall of the uterus forced him to admit the origin of the epithelial part of the adenomyoma in the epithelium of the uterus, that is to say, of Mueller's duct. This would seem to warrant a similar conclusion in the present case.

Recklinghausen mentions also another hypothesis which appears quite plausible, though it has not yet been confirmed by actual observations. The organs of Wolff and Mueller lie so close together in the early stages of embryonic life that the formation of a communication between them is quite possible. This may be preserved in extra-uterine life and give rise to communications similar to those described above. This hypothesis needs actual observation to support it, but is in itself thoroughly logical and convincing.

Summing up, we find a number of communications formed by depressions between folds of the mucous membrane of the tube, no differences in the epithelial cells of the various epithelial formations, no prearranged route of lessened resistance for cells proceeding from without inward. In the absence of further evidence I incline to the theory of a salpingogenic origin of the abnormal epithelial masses in this tube.

I have to admit that there is no evidence of a very active proliferation of the epithelium of the tubal mucosa and that the connective tissue of the mucosa shows no signs of active inflammatory or of merely congestive conditions. But as we cannot know how long before the removal of the

specimen the formation of the epithelial masses in the wall occurred, we are justified in assuming that an inflammatory or congestive condition, which has now disappeared, has at some former time existed, which at the time of its acme caused the aggressive progress of the tubal epithelium proper.

I omit the description of the other three nodules, as they present no new features.

Regarding the causation of the growths, two possibilities present themselves. The one is that the epithelial masses from the Wolffian duct were placed congenitally in the neighborhood of the tubal epithelium and have by their presence and activity caused an irritation of the surrounding muscular tissue, producing a muscular tumor. The epithelial masses must have grown simultaneously, since the widespread epithelial formations cannot be supposed to have existed in their entire extent prior to the growth of the sometimes very large tumors of this kind. The second theory is that the epithelial masses originate in the epithelium of the tube, which has taken on an abnormal growth, has invaded the wall, and by its presence and activity has led to hypertrophy of the muscular tissue. The hypertrophy of the muscular tissue may also have been caused by the same irritation which caused the active progress of the epithelium. We shall have to discuss this further after a consideration of salpingitis pseudo-follicularis.

It is evident that remnants of the Wolffian body imbedded in the wall of the tube and surrounded by an indistinctly limited myomatous growth must present a striking microscopic resemblance to the salpingitis isthmica nodosa. Schauta himself assumes that what he terms salpingitis isthmica nodosa has occasionally been mistaken for a small myoma, but the converse may also take place, and salpingitis isthmica nodosa may have been diagnosed where the condition was really one of adenomyoma of the tube. The resemblance between these two pathological conditions will even be enhanced when in consequence of supervening acute and severe inflammation considerable round-cell infiltration and the purulent disintegration of part of the tissue occur. All reports of the remnants of the Wolffian duct mention that the col-

umnar epithelium of these formations is ciliated in places, while Chiari states (1) that no cilia have been found on the columnar epithelium of the salpingitis isthmica nodosa. In my opinion, however, too much stress should not be laid on this one point, since post-mortem changes in the specimens have undoubtedly often rendered observations on this point impossible. Chiari's description is based on specimens taken from cadavers.

I examined several of Recklinghausen's cases of adenomyomas of the uterus immediately after the operation and could then distinctly observe the actively moving cilia. The tube described above as salpingitis isthmica nodosa (Case I) I examined after it had been preserved in alcohol for some time. I am unable to say whether the epithelia in the wall of the tube had no cilia or whether these very delicate structures had existed, but were destroyed in consequence of the method of preservation.

In regard to the diagnosis of adenomyoma of the tube, I should consider the following points valuable: Where inflammation of the mucous membrane of the tube is not distinctly pronounced I should be inclined to regard epithelial formations in the wall of the tube which show no connection with the epithelium of the tubal canal as belonging to remnants of the Wolffian duct, whether the muscular hypertrophy is very prominent or not. If similar epithelial formations are found in other parts of the tube or in the uterus I should consider this corroborative evidence in favor of the Wolffian duct. The remnants of the Wolffian duct and the parasalpinx can, until further material is furnished, be differentiated by the fact that the intraparietal parasalpinx forms a duct with few short ramifications, while the remnants of the Wolffian duct appear as an accumulation of many ducts and cysts. It has been mentioned above that active inflammation may obscure matters so that a differential diagnosis becomes impossible.

There is one more kind of abnormal epithelial formation in the wall of the tube which may be congenital or acquired—the peritoneal growth. The evidence seems, however, to be in favor of the latter origin, and it will therefore be discussed among the acquired conditions.

The acquired conditions to the discussion of which we now proceed, are important because they are calculated to throw much light upon the question of the causal connection between inflammation and the new formation of epithelium in and the muscular hypertrophy of the wall of the tube. Regarding these conditions I have first to mention Kaltenbach's observation (23). Kaltenbach describes a case of hypertrophy of the tubal wall accompanying inflammation of the tube. The tube was thickened to the size of the index finger and the fimbriæ were occluded. Epithelial formations in the wall of the tube are not mentioned. The thickening of the tubal wall is caused by hypertrophy of the muscular tissue throughout the wall.

A different kind of thickening of the tubal wall is described by Zweifel (24). He reports several cases of purulent inflammation of the tubal mucous membrane where the wall of the tube shows nodular enlargement. The enlargement is caused by hypertrophy of the connective tissue, and round-cell infiltration is observed between the muscle bundles, especially along the blood-vessels. Zweifel calls this condition "salpingitis interstitialis" and distinguishes from it another kind which he terms "salpingitis interstitialis disseminata." In the latter form the accumulations of round cells make up foci which are in fact small abscesses. Similar observations had been made before those of Zweifel by Martin (2) and Orthmann (25). The case described above as Case II, b, presents such an abscess. I have another beautiful specimen of this kind which I have obtained from a case of ovarian abscess and chronic salpingitis.

Case VIII. The ovary contains an abscess the size of a walnut, the tube is thickened to about twice its normal size and is very hard. I made sections through the tube, ovary and the intervening part of the broad ligament. I cannot dwell long upon the description of the ovary and broad ligament. Suffice it to say that the ovary contains beside the abscess a number of areas of round-cell infiltration and in one place an almost mature follicle with a germinative cell of absolutely normal appearance. The broad ligament contains parovarian tubules and is practically free from inflammatory nests, showing a perfectly normal meshwork of connective and muscular tissue and blood-vessels. While the observation of the normal follicle teaches an important lesson with regard

to conservative ovarian surgery, that of the normal broad ligament between an abscess of the ovary and a chronically inflamed tube cannot be disregarded by those who try to establish as an absolute rule the spreading of infection from the tube to the ovary by the way of the lymphatics of the broad ligament.

The tube itself gives evidence of chronic inflammation by the abundant round-cell infiltration of the folds of its mucous membrane. The infiltration is in some spots so abundant that the connective tissue proper of the mucous membrane is entirely covered. The epithelium is well preserved throughout the tube. The cavity of the tube is narrow, the folds of the mucous membrane are not extraordinarily numerous or large. The wall of the tube is so much thickened that it takes up about three-fourths of the diameter of the tube. The circular muscular layers are normal in extent. Wherever the connective tissue enters between the bundles of muscular tissue masses of round cells are seen which fill all the space between the muscle bundles. This round-cell infiltration penetrates beyond the circular layer and is observed in patches in the neighborhood of what appear to be lymphatic vessels in the outer layers of the tube. These outer layers present a striking appearance from the almost complete absence of longitudinal muscle fibres. The largest part of the outer layers is composed of connective tissue. The subserous layer of the tube contains larger masses of round cells, fewer, however, than the mucous membrane or the muscular layer next to it. A membranous adhesion is seen starting from the serous surface of the tube. The bulk of the enlargement of the wall is caused by the development of the connective tissue. No epithelial masses are to be seen outside the mucous membrane.

This is a well-marked case of salpingitis interstitialis. It is important in more than one respect. For instance, the distribution of the round cells is quite significant as to the spreading of the inflammatory process. The most natural explanation is as follows: The inflammation has proceeded from the uterus into the tube, as is witnessed by the inflammatory infiltration of the mucous membrane and its immediate surroundings. From here the inflammation has not passed through the wall of the tube, as is proven by its absence in the middle part of the tubal wall. The inflammation has spread through the abdominal end into the ovary, causing abscess of the same, and into the serous coat of the tube, causing infiltration with round cells and the formation of bands of adhesion.

A condition which has been mentioned repeatedly and is of the greatest importance in the discussion of our subject has been described by Martin (2) and Orthmann (25) as "salpingitis follicularis," or, as Martin calls it more correctly in his recent treatise on the diseases of the tubes (26) "salpingitis pseudo-follicularis." Both of these authors, as well as several others, have described cases of this disease without specially mentioning the occurrence of nodules. A case which I partly described above (Case VI, a) belongs to this category.

Case VI, b. The tube is almost perfectly straight without any tortuosities. The abdominal end is open. The tube is thickened to the size of the index finger. The tissue of the wall occupies about one-half the diameter of the tube. The wall is composed mainly of connective tissue, while the circular and longitudinal muscular layers are thin. The mucous membrane of the isthmic part does not present the normal numerous ramifying folds, but the cavity is surrounded with four to six broad elevations of the mucous membrane. These elevations contain numerous cyst-like cavities, some of which are as large as a grain of mustard-seed. The larger ones contain an amorphous granular mass. These cavities as well as the main cavity of the tube are lined with the normal tubal epithelium. The cavities contained in the elevations of the mucosa can be proven by serial sections to communicate with each other and with the main cavity by numerous small openings sometimes formed like ducts. They are therefore not real cysts, but dilated depressions between the folds of the mucosa. The connective tissue of the mucosa shows in many spots hæmorrhagic infiltration and pigmentation. This hæmorrhagic infiltration accompanies a continuation of the mucous membrane which penetrates into the wall of the tube. In some specimens this continuation extends from the mucosa proper through the circular and longitudinal muscular layers into the subserous tissue of the tube. A number of epithelial ducts with numerous ramifications are seen lying side by side outside the mucosa proper. They are lined with epithelium similar to that which covers the tubal mucous membrane and are imbedded in a connective tissue which presents such marked hæmorrhagic infiltration and pigmentation that it can be seen even macroscopically. The direction of this continuation of the mucous membrane is towards the upper border of the tube. The extent of this formation in a longitudinal direction is not more than a few millimetres. There is no connection between this system of epithelial formations and the one described under Case VI, a. The connective tissue surrounding the para-

salpinx (Case VI, a) contains no trace of the hæmorrhagic infiltration, which however follows the other epithelial formations.

There are no symptoms of acute inflammation, but the hæmorrhagic infiltration and the conglutination of the folds of the mucous membrane give sufficient evidence of a chronic inflammatory process.

This case is a typical one of salpingitis pseudo-follicularis, as the formation of the cyst-like cavities of the mucosa and the epithelial formations in the wall prove. For the connection of the latter with the mucosa proper direct evidence is given above. But it cannot be gainsaid that, if a more acute inflammation had set in giving rise to abscesses in the wall, the proof of the connection between the two epithelial systems might have been lost, so that an appearance identical with the one described as salpingitis isthmica nodosa would have been created. I am well aware of the fact that the pigmentation of the connective tissue surrounding the epithelial formations has been regarded as characteristic of remnants of the Wolffian body. But in view of the communication between the cavity of the tube and the epithelial formations, I regard the diagnosis of salpingitis pseudo-follicularis as firmly established.

The penetration of epithelial ducts into the wall of the tube, strange as it may at first appear, is not without parallel in other organs, more especially in the generative organs themselves. It is a well-known fact that under inflammatory irritation the glands of the mucous membrane of the uterus, both of the neck and body, hypertrophy to such a degree that they enter between the bundles of the muscular tissue, so that even doubts as to the benignant or malignant nature of the process may arise. The presence of a layer of connective tissue around the epithelial formations, however thin it may be, must be regarded as a proof of the benignancy of this condition.

Two observations similar to those described above have been made by Werth (14) in cases of extra-uterine pregnancy. I mention just this one author on account of the importance which he attributes to the salpingitis pseudo-follicularis with regard to the causation of extra-uterine pregnancy. He thinks it would be a very remarkable chance indeed if an ovule on its way through such a tube was not caught in

one of these recesses. Regarding the origin of the recesses, he shares Martin's opinion.

It must necessarily be very difficult to make a differential diagnosis between such a salpingitis pseudo-follicularis and the cases termed salpingitis isthmica nodosa. The explanations of the origin of both as given by their first observers are absolutely identical, and among more recent authors Reymond (27) fully shares this opinion. Both conditions are ascribed to an abnormal growth of the tubal epithelium caused by inflammatory irritation. The abscesses which are found in some cases of salpingitis isthmica nodosa and which are not mentioned in the descriptions of the salpingitis pseudo-follicularis are not at all characteristic. Schauta himself declares (3) that they are sometimes absent in cases of salpingitis isthmica nodosa. A case of salpingitis pseudo-follicularis with acute inflammation and consequent round-cell infiltration and destruction of the epithelium would indeed cause insurmountable difficulties in regard to differential diagnosis. This seems to explain why Schauta could describe 18 cases of salpingitis isthmica nodosa (though he gives an anatomical description of but two); while on the other hand Martin describes a number of cases of salpingitis pseudo-follicularis and finds the salpingitis isthmica nodosa remarkably rare among his own cases. Chiari (1), as mentioned above, considered these cases to be practically identical with salpingitis pseudo-follicularis, and it was only Schauta who would regard them as a separate pathological entity.

It is an attractive, even though ungrateful task, to enquire into the process of the growth of such epithelial formations. Our knowledge of the mechanism of cell-growth is in its very infancy, and guess-work and speculations without any solid foundation will not further us. It may therefore not be amiss to point out at least as much evidence as we possess. As the cases of salpingitis pseudo-follicularis occur in non-occluded as well as in occluded tubes, accumulations of any kind cannot be the effective cause of the penetration of the epithelia into the wall. Pressure of the contents would rather tend to produce epithelial atrophy, as the observations on hydro- or pyo-salpinx, hydro- or pyo-metra, and hydro- or pyo-nephrosis prove. Active proliferation

of the epithelia, however, would offer quite a satisfactory explanation. It will be our future task to prove this on specimens which have to be subjected to the proper methods of preservation before death sets in in the tissues.

We are confronted with peculiar difficulties when we proceed to the consideration of the last kind of epithelial formation which we have to discuss here. The English and American literature contains nothing about them, and even among the German medical papers the reports of such formations are few and far between.

I have met this last kind of epithelial formations, which I shall term "peritoneal growths," in a number of cases where there have been peritoneal adhesions or pseudo-membranes covering the pelvic organs. It would lead us too far to consider here all the relations of these peritoneal growths to the question of inflammation of the serous membranes. Suffice it to mention that the text-books of pathology, for instance, those of Ziegler and Orth, refer to swelling, detachment and fatty degeneration of the peritoneal endothelium in chronic peritonitis and ascites. Klebs (28) describes superficial cysts of the broad ligaments, the origin of which may, according to him, be found in the germinative epithelium of the ovary. Fabricius (29) in a recent paper shares this opinion. Waldeyer (30) explains them as remains of germinative epithelium which have become covered with connective tissue. Pfannenstiel (31) connects their origin with ovarian cystomas, which existed in his cases.

Klob (32) describes papillary growths on the serous coat of the tubes, the larger ones among which become hollow and form real cysts. Walker (33), Dobbert (34), Zweifel (35), Werth (14), Zedel (36), and others have described in cases of extra-uterine pregnancy formations apparently identical with those to be reported here. They always connected them with the pregnancy, but my cases prove clearly that pregnancy has nothing to do with these formations, at least not directly, though in those cases where it produces adhesions and pseudo-membranes, pregnancy may act as an indirect factor.

Of the two cases in which I found the most beautiful development of these peritoneal growths, one has been partly described above (Case

II). The other case is one of chronic interstitial salpingitis, very much like Case VIII (see above). In addition, the tube presents under its serous surface a number of small cysts, the largest ones of which are about 5 mm. in diameter. The cysts partly protrude on the surface of the tube and partly are situated in its wall without changing the normal outline of the tube. The abdominal end is open.

I shall not go into a detailed description of these two specimens and of those from all of the other cases in which I found the same condition though less developed, but will leave this for some future opportunity. I shall give here only the results of my observations and my conclusions.

I find in cases where the tube is covered with pseudo-membranes peculiar accumulations of epithelioid cells which are generally covered by the pseudo-membranes and reach the surface at only a few points. These points are, however, observed in sufficient numbers to suggest the theory that the peritoneal surface is the starting point of these formations. The pseudo-membranes themselves are always largely made up of hæmorrhagic tissue with numerous pigment cells. It is generally possible to distinguish the original surface of the tube, and only in a few places the connection between tube and pseudo-membrane is so intimate that it becomes impossible to tell where the tubal tissue ends and the pseudo-membrane begins. The tubal tissue under the pseudo-membrane generally shows more or less dense accumulations of round cells.

The border-line between tube and pseudo-membrane is always most distinct where it is formed by the epithelioid cells. These cells have this in common, that they generally occur or at least originate in more or less wide and straight or irregular clefts and chinks between tube and adhesion membrane. These clefts sometimes assume irregular shapes with sharp angles corresponding to sharp bends and slight strangulations of the tube. In other cases the clefts form for long distances straight lines. The straight clefts as well as the larger and more irregular crevices frequently communicate with the surface through narrow or wide gaps or duct-like openings.

The epithelioid cells investing these chinks vary considerably in

size and appearance. Some are flat and large, resembling the endothelial cells lining lymphatic vessels, the nucleus of the cell producing a protuberance on the outline of the cell. Others are more cuboidal, the nucleus filling a large part of the cell, and still others are cylindrical, looking precisely like the epithelia of the tubal mucous membrane. The surface of the cuboidal and cylindrical cells is usually slightly convex, the nucleus is always large and contains one or several nucleoli. The cells, and especially the nuclei, stain very readily. I have never met with cilia or karyokinetic figures, but none of the specimens have been preserved with special regard to this point. The different kinds of epithelioid cells frequently occur together in one group; others are mainly made up of one kind of epithelium. As the cells look in many places absolutely like the epithelia of the tubal mucous membrane, one would like to call them epithelia, but with regard to their origin and their different appearance in different places it will be best to call them "epithelioid," thereby avoiding the notion of a true epithelial nature.

I have been able to distinguish four different types of epithelioid formations composed of such cells. The intermediate types are observed sufficiently frequently to establish their connection.

The first type of epithelioid formations is found in long, straight, narrow clefts between tubal tissue and pseudo-membrane. The cleft is lined on one or both sides with cuboidal cells in one row. Where the cleft is tapering, the cells are more flat and of the endothelial type. In some clefts where there is only one row of epithelioid cells—and this one always on the tubal side—the cells do not terminate at the end of the cleft, but pass from the tubal side of the cleft over to the pseudo-membrane and invest it for a certain distance. In others the epithelioid cells invest both sides of the cleft. The cleft sometimes has no contents; in other places it contains amorphous detritus (Plate XXXII, Fig. 2). This type is an exact counterfeit of the growths of germinative epithelium described on the ovary under pseudo-membranes by Nagel (37) and others.

In the second type there is instead of the single row of cells, characterizing the first type, a solid accumulation of cells with more or

less rounded outline and sometimes tongue-like processes penetrating the surrounding tubal tissue. The cells composing this accumulation are square or multangular. Round cells sometimes surround these solid bodies to a great extent and invade even the epithelioid masses. Intermediate stages between the single rows and the multiple layers are frequently seen (Plate XXXII, Fig. 3).

A different kind of growth of the single rows of cells (type 1) leads to the formation of type 3 (Plate XXXII, Fig. 4). Here the cleft is wider than in type 1, and is filled partly with detritus partly with epithelioid cells of a peculiar arrangement. On superficial inspection there seem to be irregular worm-like coils of epithelioid cells arranged in the manner of a papillomatous growth, but on closer examination the condition proves to be entirely different from that of a papilloma. The epithelial elevations contain no connective tissue; they consist merely of epithelioid cells which sprout forth like buds. As Fig. 4 shows, such an epithelioid bud sometimes starts from just one epithelioid cell on the wall of the cleft. Before the buds attain the opposite wall they arrange themselves in coils and may then form smaller or larger solid epithelioid masses. It is peculiar to this type that the epithelioid buds may fill the clefts but do not invade the surrounding tissue. In the course of their development one bud can at last fill the whole chink as a solid roundish body attached to the wall by a very thin pedicle. If the section does not happen to be laid just through the pedicle, one sees a solid epithelioid mass separated all around by a very narrow cleft from the epithelioid cells investing the original outline of the cleft. The cells lining the cleft are cuboidal or flat (Plate XXXII, Fig. 6); the cells composing the solid masses are generally large and multangular.

In the solid masses of both types 2 and 3 a certain condition is observed in many places which characterizes it as an intermediate stage between these types and type 4. This intermediate stage shows vacuolization of the solid masses in varying degrees. In some places there is a vacuole in only one cell; in others the vacuoles are larger and are contained between the cells. Some of the solid bodies contain three, four, or even more vacuoles, so that at last the mass looks worm-eaten or honey-combed (Fig. 6). The vacuoles frequently have

no contents, at other places, especially where they are large, they contain detritus and detached and (as is shown by their failure to take the stains) degenerated epithelioid cells.

The terminal stage after the disappearance of all dividing walls between the vacuoles is seen in type 4 (Fig. 5), a round or oblong cyst. The epithelioid cells lining the cyst are not always arranged in the same way. Sometimes there is only one row of cells, which are exactly like the high cylindrical cells of the tubal mucous membrane; in other cases the cyst is lined with several layers of flat cells; in other cases, again, the cyst itself is surrounded by one row of cylindrical or cuboidal cells, which in its turn is separated by a very narrow cleft from a circle of flat cells. It is superfluous to enter further into the details of the development of each of these cystic formations after what has been said above about the intermediate stages. The cysts almost always contain some detritus and large vesicular, detached and degenerated epithelioid cells. The cysts are of various sizes; some are microscopic, while others form protrusions under the serous coat which can be seen with the naked eye. The tissue separating these cysts from the serous surface is frequently extremely thin.

The bulk of these epithelioid masses does not generally contribute very much to the enlargement of the tube, but where the tubal wall is very thin in consequence of atrophy of the muscular tissue in it, as for instance in Case II, the epithelioid masses form a large part of the wall of the tube. They are then to be found throughout the wall of the tube, and not only immediately under the pseudo-membranes.

While the histological description of these four types and their consecutive development is simple, an effort to arrive at a satisfactory theory as to their origin meets with somewhat greater difficulties. In considering the pathogenetic process, five different modes of origin have to be discussed. The starting point of these growths might be sought in:

1. remnants of the Wolffian body,
2. aberrant tubes, parasalpinx,
3. the endothelium of lymphatic vessels,
4. the peritoneal endothelium,
5. the germinal epithelium.

The origin from the epithelium of the tubal canal can be excluded, as there is never found a communication between the cavity and the above-mentioned epithelioid formations. Remnants of the Wolffian body have a uniform true cylindrical epithelium, a sheath of connective and frequently of muscular tissue; they do not form solid epithelial masses. All of these signs tend to prove that the epithelioid masses cannot be derived from remnants of the Wolffian body. The same conclusion holds good with regard to the parasalpinx, which forms one or two isolated epithelial tubes in the wall, but does not by any means extend over the entire circumference of the tube as the epithelioid formations may do.

The endothelium of lymphatic vessels cannot be excluded with the same ease. The low and flat cells of the first type described above look very much like endothelia, and observations on pathological growths originating in the lymphatic endothelia, the endotheliomas, prove that endothelial cells may become so similar to true epithelia that they cannot be differentiated by their shape. On the other hand the entire absence of dichotomic formations speaks against an origin from the lymphatic capillaries. The absence of dichotomic formations and of the arrangement of the epithelioid masses in the manner of strings of beads is certainly opposed to the hypothesis of a secondary invasion of the lymphatics.

The fourth possibility mentioned above appears to approach the truth more nearly than any of those as yet mentioned. When pseudo-membranes form on an organ lined with a serous coat—be it peritoneum or pleura or pericardium—the endothelia of these serous coats either degenerate entirely and disappear or they become included between the organ and the pseudo-membrane. Being thus in a condition of "relative heterotopy," as it might be termed, they participate in the developmental possibilities common to all cells which have become deprived of their original standing in the system. They become subject to abnormal growth and to degenerations of various kinds. Under these conditions swelling and enlargement of endothelial cells is quite a common occurrence. As the communication of the epithelioid masses with the peritoneal surface can be observed directly; as

the luxuriant growths of type 3 are observed in those larger crevices on the original surface of the tube which represent secluded parts of the peritoneal cavity; as the growth and degeneration of the epithelioid masses is in perfect accordance with our knowledge of such processes in the endothelia of serous membranes, the theory that these epithelioid masses are the offspring of the peritoneal endothelium appears to furnish the best claims to acceptation. The peritoneal endothelium would, according to this theory, almost reassume an activity which it normally possesses only in the embryonic stage, where the cells lining the coeloma grow so exuberantly that they lead to large epithelial formations.

While this is by no means impossible, it must not be overlooked that the facts allow of another explanation. If by an irregular development some aberrant patches of germinative epithelium had been formed on the serous surface of the tube—a fact to the possibility of which the observations of Thiry (38) and Morau (39) seem to point—these patches may in analogy with other irregular fœtal formations preserve their energy in a latent condition until a late stage. Under the influence of inflammatory irritation they may begin to grow and may then give rise to such formations as were described above.

These last sentences contain many hypothetical statements. Furthermore, the various shapes of the epithelioid cells are rather against this theory. The fact, however, that conditions similar to those of type 1 have been described on the ovary, Nagel (37), where their origin must be ascribed to the germinative epithelium would induce one to regard such a process as not beyond all likelihood.

It has been suggested by Fabricius (29) that there is another way in which germinative epithelium may appear on the surface of the tube, namely, in consequence of adhesions between ovary and tube which occur frequently in inflammation of the uterine appendages. In the cases described by Fabricius it was difficult to exclude this, since this author made his observations on cases in which tube and ovary were bound together by adhesions. But in my cases there were no such adhesions between ovary and tube, and this origin of the epithelioid masses can, therefore, be excluded with certainty. It seems

to me most probable that the endothelium of the peritoneum itself is the starting point of the epithelioid masses under discussion.

It would lead us too far to discuss the importance of these observations with regard to the questions of chronic peritonitis and small cystic formations on the peritoneum. But it is necessary to draw attention to another question which presents itself here. It might be asked: Is it not possible that the epithelial formations, described above as salpingitis pseudo-follicularis or salpingitis isthmica nodosa or as intraparietal parasalpinx, originate in these peritoneal growths? But though doubts may arise in some complicated cases, in general it may be said that the extent of the peritoneal growths over a very large part of the tubal circumference is sufficient to differentiate these growths from the more isolated epithelial growths of the salpingitis pseudo-follicularis or the intraparietal parasalpinx. Besides it can hardly be expected that the peritoneal growths which produce more or less extensive epithelial formations in the wall of the tube would vanish so absolutely as to leave hardly any trace of their primary existence. And the fact is that neither in a case of intraparietal parasalpinx nor in one of salpingitis pseudo-follicularis could I discover peritoneal growths of any extent.

After the description of these specimens we find ourselves confronted with an unexpected state of affairs. The conception of a peculiar pathological condition designated by the term "salpingitis isthmica nodosa" seems to disappear entirely. We started from a condition of nodular enlargement of the isthmic part of the tube caused by muscular hypertrophy and cystic epithelial formations in the wall of the tube. We have been able to confirm the existence of such a condition, but we have not been able to find any gross characteristic by which we might differentiate it from salpingitis pseudo-follicularis and salpingitis abscedens. Again, the rest of the described cases tend to prove that under the designation of salpingitis isthmica nodosa quite a number of different pathological conditions have been rubricated. We see nodules of the isthmic part without hypertrophy or cystic formations, where from outward appearances we should conclude that we have to deal with a genuine salpingitis isthmica nodosa. Schauta him-

self states that the nodules of the salpingitis isthmica nodosa have not invariably the same structure. What then shall we call a salpingitis isthmica nodosa? Is every nodular enlargement of the isthmic part of the tube a salpingitis isthmica nodosa? Certainly this cannot be Schauta's opinion. He says that the muscular hypertrophy and the epithelial formations may be absent. The only remaining characteristic symptom would then be the nodular enlargement. But this, as I have shown above, may be caused by a number of pathological conditions, some of which, for instance the adenomyomas, can certainly not be called instances of salpingitis, that is of inflammation of the tube.

It would therefore seem to be evident that nodules of the tube may be due to different inflammatory or non-inflammatory causes:

1. Non-inflammatory nodules:
    a. Adenomyomata.
    b. Intraparietal hydroparasalpinx.
2. Inflammatory nodules:
    a. Salpingitis catarrhalis.
    b. Salpingitis pseudo-follicularis (salpingitis isthmica nodosa).
    c. Salpingitis abscedens (salpingitis interstitialis, interstitialis disseminata).
        1. Specifica (tuberculosa, gonorrhoica).
        2. Non-specifica.
    d. Peritoneal growths (solid or cystic).

It will be borne in mind that the nodules of which we are speaking here are all produced by a circumscribed thickening of the wall of the tube. The nodular enlargements which are caused by strangulations of a dilated tubal cavity filled with pus are not considered in the present paper, whether the strangulations be caused by adhesion bands or are the result of the congenital anomaly described by Freund (40).

The nodular enlargements of the wall are not confined to the isthmic part of the tube, not even those which present a microscopic condition identical with the one described by Schauta. It is therefore unwarranted to consider those of the isthmic part of the tube as belonging to a separate pathological entity.

The causes of enlargement of the tubal wall vary considerably. In the non-inflammatory nodules a neoplasm is imbedded in the wall, while in the rest of the cases the wall is thickened in consequence of inflammatory changes, primary or secondary, in one or several tissues of the tubal wall.

Primary inflammatory thickenings are those caused by catarrhal salpingitis (enlargement of the mucosa) and the various kinds of salpingitis abscedens (thickening by inflammatory products). Secondary thickening is caused by salpingitis pseudo-follicularis (secondary growth of the epithelia under inflammatory irritation) or by the peritoneal growths (in cases of primary perisalpingitis).

I am well aware of the fact that such a division into primary and secondary conditions is somewhat diagrammatic, but even so it will help to make clear the wide differences in the pathology and pathogenesis of the conditions under discussion.

I wish to emphasize the fact that the various pathological conditions which may produce nodular enlargement by no means do so invariably. There is not one of the conditions described above which may not occasionally exist without producing an enlargement visible on gross examination. The size of the nodule is naturally of no diagnostic importance whatever. Salpingitis abscedens, for instance, may in one tube cause an even thickening, while in the other tube of the same case it may by the formation of abscesses produce a nodule of any portion of the tube, not excepting the isthmic part. It would be misleading and absolutely incorrect to term the disease of one side salpingitis abscedens and the disease of the other salpingitis isthmica nodosa, though Schauta's description of the varying histological conditions in salpingitis isthmica nodosa would fully warrant such a procedure.

CONCLUSIONS.

The conclusions at which we arrive are the following:

1. Nodular enlargement of the tube can be caused by a number of different pathological conditions.

2. Clinical examination does not enable us to make a diagnosis of the pathological condition existing in an individual case of nodule of the tube.

3. The diagnosis of the nature of a tubal nodule can be made only with the microscope.

4. The conditions causing nodular enlargement of the tube are congenital or acquired, non-inflammatory or inflammatory.

5. Any one of these conditions can exist without the production of nodules.

6. The nodules can be found in all parts of the tube and—taking the peculiar anatomy of each part of the tube into account—show the same structure.

7. The enlargement can be caused by epithelial or epithelioid formations, connective or muscular tissue, by round-cell infiltrations or combinations of two or more of these.

8. The epithelial formations originate in the epithelium of

a. the tubal mucous membrane (salpingitis pseudo-follicularis, adenomyoma originating in the tubal epithelium).

b. the accessory tubes (intraparietal parasalpinx and hydroparasalpinx).

c. remnants of the Wolffian body (adenomyoma).

9. The epithelioid formations originate in the peritoneal endothelium (peritoneal growths under " relative heterotopy ").

10. The excess of formation of connective tissue is a consequence of inflammatory conditions of the tubal wall (salpingitis interstitialis, Zweifel).

11. The hypertrophy of the muscular tissue is

a. non-inflammatory (adenomyoma).

b. consequent upon inflammation—Kaltenbach's case (23).

12. The accumulations of round cells are direct evidence of inflammation:

a. non-specific (salpingitis interstitialis disseminata, salpingitis abscedens); or

b. specific (salpingitis tuberculosa or s. gonorrhoica).

13. The epithelioid formations can occur wherever pseudo-membranes cover organs lined with a serous coat.

14. Extra-uterine pregnancy (abdominal or tubal) produces epithelioid formations by causing pseudo-membranes to form—not by any irritation peculiar to the pregnancy.

DESCRIPTION OF PLATE XXXII.

Fig. 1.—Case 1 (about 40 diam.). The figure shows about one-half of a section of the tubal nodule. *T*, cavity of tube; *A*, abscess with central cavity; *E*, epithelial formations at periphery of abscess.

Figs. 2-6.—Peritoneal growths. *S*, surface of tube (about 300 diam.).

Fig. 2.—*a*, double rows; *b*, single row of epithelioid cells. Type 1.

Fig. 3.—*sm*, solid mass of cells; *rc*, round-cell infiltration. Type 2.

Fig. 4.—*eb*, epithelial buds; *c*, capillary. Type 3.

Fig. 5.—*e*, epithelial lining of cyst; *d*, detached epithelial cells; *hp*, hæmorrhagic and pigmented tissue of the adhesion membrane; *rc*, round-cell infiltration. Type 4.

Type 6.—*a*, vacuoles. Intermediate type between types 3 and 4.

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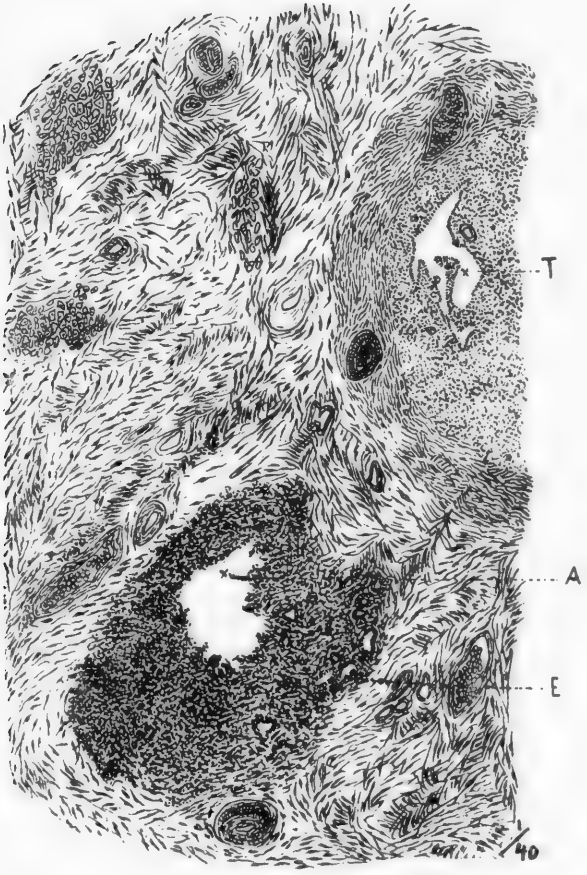
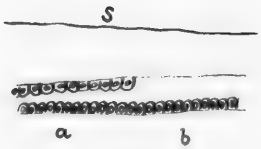


FIG. 1.



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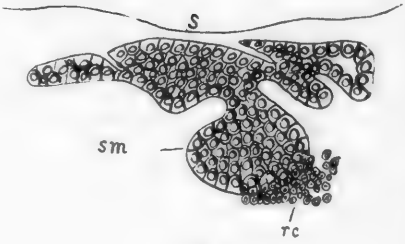

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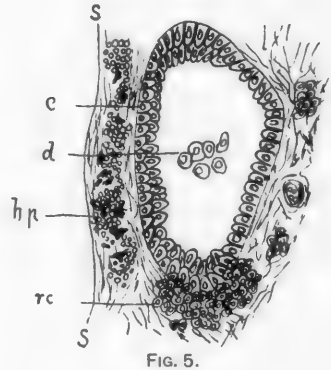

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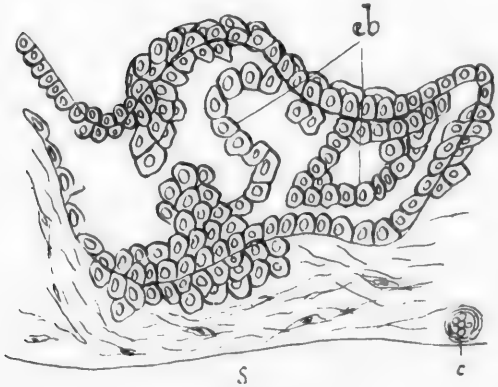

FIG. 4.

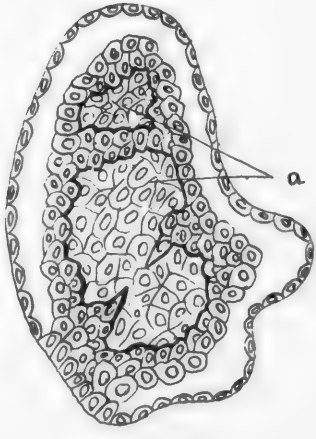

FIG. 6

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ON THE CAUSE OF THE HEART BEAT.*

By W. T. PORTER.
(*From the Laboratory of Physiology in the Harvard Medical School.*)

A few years ago the writer of this paper published in Pflüger's *Archiv* (1)† an account of some experiments directed against the idea that the beat of the vertebrate and especially the mammalian heart is caused by rhythmic impulses discharged by a narrowly circumscribed group of nerve cells (2). These experiments consisted in the making of infarcts in the dog's heart by keeping the animal alive after the ligation of one or more of the main coronary arteries. It was found that all parts of the heart could be successively infarcted, in a series of animals, without arresting the contractions. The knowledge that the muscle fibres in an infarcted area show signs of death soon after ligation of their supplying artery (3) justified the assumption that the cardiac nerve cells, confessedly more highly differentiated than the muscle fibres, would rapidly perish when deprived of their blood supply. From these premises was made the deduction that hearts which carried on their work in the living animal hours and even days after the infarction of a vascular area could not be dependent for their contraction on nerve cells situated in the infarcted area itself. As any part of the ventricle may be thus infarcted without stopping the contractions of the heart, it follows that the cause of the contraction cannot be the discharge of rhythmic impulses from a narrowly circumscribed group of nerve cells lying at some definite point in the ventricular septum.

In searching for a further proof of the incorrectness of the circum-

* The results of these experiments, except that of April 21, were laid before the Boston Society of Medical Sciences, March 30, 1897, and an abstract was published in No. 10 of the *Journal of the Boston Society of Medical Sciences*, March 30, 1897. The full paper was presented at the meeting of the American Physiological Society in Washington, May 5, 1897.

† References to literature are at the end of this article.

scribed-co-ordination-centre hypothesis, it occurred to me that the parts in which these centres are supposed to lie might be cut out of the heart without stopping its contractions, provided the nutrition of the remainder of the heart was maintained. On March 22, 1897, this idea was put to the test. The isolated heart of a cat (4) was made to resume its regular contractions by feeding the coronary arteries through the aorta with defibrinated cat's blood. While the heart was in full play the right ventricle was separated from the left and the interventricular septum cut out. Both right and left ventricles continued their rhythmic contractions.

Two days later a more extended experiment was made. A cat's heart was cut out of the body and fed through the coronary arteries with cat's blood diluted with 0.8 per cent sodium chloride solution. Co-ordinated contractions were secured. The right ventricle was then almost wholly separated from the left, yet both ventricles continued to beat in unison. The interventricular septum was now extirpated. Still both ventricles continued to beat. On slitting each ventricular portion from apex to base, the incisions being carried almost to the auricles, the four pieces beat synchronously.

On the afternoon of that same day a step farther was taken. A cannula was tied into the circumflex branch of the left coronary artery in the heart of a cat, and the portion of the ventricle supplied by the circumflex cut out. On feeding this extirpated piece with defibrinated cat's blood through its nutrient artery, rhythmic contractions of parts of the fragment were obtained. At first a papillary muscle contracted regularly; later this ceased, and another part of the wall took up the contraction.

Two days thereafter, a cat's ventricle which had been cut into strips in the manner described in the first experiment of March 24, contracted strongly for two and three-quarter hours, and feebly for three-fourths of an hour longer. Graphic records were taken from this heart with an ordinary muscle lever fastened to the end of one of the ventricular strips.

The experiments were now transferred to the dog.

On March 27, 1897, a dog weighing 10 kilogrammes, anaesthetized

with morphia and ether, was bled from the left carotid artery, and the blood whipped, strained through glass wool, and diluted with an equal volume of 0.8 per cent normal saline solution. Normal saline of the same strength, made with tap water, and having a temperature of about 36° C., was meanwhile allowed to flow into the right jugular vein. After a short interval the dog was again bled from the carotid artery. The product of these bleedings was mixed and placed in a reservoir at the temperature of the body. The heart was now extirpated, a cannula tied into the ramus descendens of the left coronary artery, the interventricular septum and the auricles completely cut away, and all the ventricle removed except that portion supplied by the descendens itself. The cannula was then connected to the reservoir of warm blood mixture, and the piece of ventricle perfused with the blood at a constant pressure, which to begin with was about 30 mm. Hg., but which was afterwards raised to 90 mm. Hg. The blood entering the cannula was bright arterial red; that emerging by the coronary vein was venous blue. In a few moments the ventricle began to beat with great vigor, shortening about seven millimetres in vertical diameter. An ordinary muscle lever, magnifying eight times, and weighted with 40 grammes, was fastened to a hook thrust through the apex, and recorded curves about 50 mm. in height. The curves showed some irregularity both in force and frequency. The ventricle beat more rapidly when surrounded with blood at the temperature of the body than at room temperature, but the character of the contractions remained unchanged. At 1 P. M., after writing curves for one hour, the ventricle was thrown into strong fibrillary contractions by stroking its surface with the electrodes of a Du Bois-Reymond induction coil (tetanic stimulation). Five minutes later good co-ordinated contractions returned. Forty minutes thereafter the ventricle was thrown a second time into fibrillary contractions, from which it soon recovered. Two and three-quarter hours after the ventricle began to beat the experiment was broken off. The contractions were by this time very feeble, but still unmistakably co-ordinated.

Experiments similar to this were repeated on five dogs and three cats, and showed that any part of the ventricle will beat rhythmically

when supplied with the animal's own blood at a normal temperature and pressure. Even pieces cut off roughly and left lying on the table for an hour may give strong and long-continued rhythmical contractions when fed with blood. Occasional failures occur, but these are exceptions. The return of rhythmical contractions is secured in the greater number of experiments.

It follows from these experiments that: (1) *The cause of the rhythmic contraction of the ventricle lies within the ventricle itself.* (2) *The cause of the rhythmic contraction is not a single localized co-ordination centre; the co-ordination mechanism, whatever it may be, is present in all parts of the ventricle.* (3) *The integrity of the whole ventricle is not essential to the co-ordinated contraction of a part of the ventricle.*

It should be pointed out that long-continued spontaneous contractions of the completely isolated ventricle are here secured for the first time. The methods employed by Wooldridge and Tigerstedt (5) to isolate the ventricles were incomplete, in that a part of the auricles was left attached to the ventricles. The ligature used by Wooldridge, and the atriotome employed by Tigerstedt, cannot be applied in such a way as to entirely separate the auricles from the ventricles (6) without compressing the coronary vessels in the auriculo-ventricular furrow, and thus interrupting the blood supply on which the continued action of the ventricles depends.

I have already said that any part of the ventricle of the dog or cat will beat rhythmically. The "apex" of the ventricle is no exception to this rule. Contrary to the present universal belief of physiologists, it is not impossible, but easy to secure rhythmic, long-continued, spontaneous contractions from the wholly isolated "apex" of the mammalian ventricle, as the following experiments will show.

On March 29, 1897, the heart of a dog, prepared as in the experiment of March 27, was cut out and a cannula tied into the ramus descendens of the left coronary artery not far from the apex of the left ventricle. That part of the apex which could be fed through the cannula was then excised. Both apex and basal portion fibrillated. The septum was removed. The piece of ventricle secured was 28 mm.

in length (*i. e.*, in the direction from the base to the apex), 23 mm. broad opposite the end of the cannula, and 27 mm. broad at the somewhat flattened tip of the apex. The ventricle measured from base to apex 70 mm. The part cut out was, therefore, the part which all observers (except Berkley) believe to be lacking in nerve cells. The cannula was now connected with the blood reservoir and the apex perfused with blood. In a few moments regular and strong contrac-

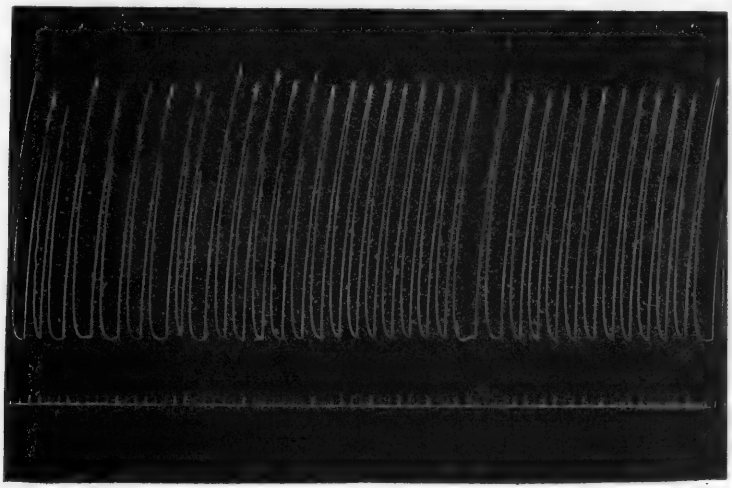


Fig. 1.—From the experiment of March 29, 1897. Curves drawn by a muscle lever, magnifying 8 times, attached to the apical two-fifths of a dog's ventricle, which had been cut away from the remainder of the ventricle, and was supplied with defibrinated dog's blood through a cannula in the descendens artery. The lower line gives the time in seconds. The temperature of the extirpated piece was about 30 C. On raising the temperature to 37 C., the character of the contractions was unchanged, but their frequency was much increased.

tions set in. Curves were recorded with an ordinary muscle lever (Fig. 1). During systole more blood escaped from the veins than during diastole. The experiment was stopped after the apex had contracted one hour and forty minutes. During a part of this time the preparation was in a bath of blood at the temperature of the body.

On April 5, the apical 10 mm. of a dog's ventricle (*i. e.*, the ten millimetres nearest the apex, measured on the long axis of the ven-

tricle) was perfused by the method described above and gave strong rhythmical contractions during several hours.

These experiments demonstrate that *the "apex" of the mammalian heart possesses rhythmic contractility.* Further, assuming that the general belief in the absence of nerve cells from the apical portion of the ventricle is correct, they demonstrate that *nerve cells are not essential to long-continued, rhythmic, co-ordinated contractions of the ventricle.*

The revision which these observations necessitate in the present teaching regarding the causation of the heart beat is evident. Physiologists, as is well known, are at present divided into two schools, the one holding to the classic doctrine that the heart is made to contract by impulses discharged by the nerve cells within its walls, the other maintaining that the contractions are produced by the rhythmic contractility of the cardiac muscle fibres (7).

The nerve-cell hypothesis is attacked on the ground that the rhythmically contracting hearts of many lower forms, *e. g.*, the gastropods, have no nerve cells at all (8), and on the ground that the heart of the mammalian embryo beats with faultless rhythm many hours before nerve cells have settled in its walls (9). To these powerful arguments are added others of probably subsidiary value. In the frog the cardiac contraction begins in the great cardiac veins and extirpated pieces of these veins, in which microscopical examination has thus far failed to show nerve cells, give rhythmic contractions (10). The apex of the batrachian heart, believed by all observers (except Berkley) to be wanting in nerve cells, will contract rhythmically when subjected to a constant stimulus, such as the galvanic or faradic current, pressure on the endocardium, poisons and various chemical agents, perfusion with old blood, and suspension for several hours in a moist chamber.

In answer to these arguments, the advocates of the nerve-cell theory reply that no conclusion as to the rhythmic contractile power of the adult heart can be drawn from the embryonic heart, because it is well known that fully differentiated adult tissues lose many of the attributes of embryonic tissues. The behavior of the crustacean heart is no criterion for the mammalian or even the batrachian heart, because of

the profound phylogenetic gap between them. Moreover, the alleged absence of nerve cells from the hearts of these lower forms rests, for the most part, on studies made with histological methods less perfect than those employed at the present day. This older teaching has been in part already overthrown (11). As to the "ganglion free apex," the experiment of Bernstein (12) is conclusive. By ligating or squeezing the frog's ventricle across the middle with a pair of forceps, the tissues at the junction of the basal and apical portions of the ventricle can be crushed to the point at which physiological connection is destroyed, although physical continuity is still preserved. Such frogs have been kept alive as long as six weeks. Only exceptionally does the apex beat again. Finally, that the apex should contract in response to a constant stimulus is not surprising; even curarized, striated muscle contracts more or less periodically when placed in certain saline solutions (13). No one concludes from this that these striated muscles contract rhythmically under normal conditions in the body. Why then should this conclusion be drawn from a similar experiment performed on the heart muscle (14)?

Plainly the crucial point in this controversy is whether the apex, a part of the ventricle believed to be lacking in nerve cells, can be made to give long-continued, rhythmic, spontaneous contractions. If the apex will do this, and if this part of the heart really contains no nerve cells, it is certain that nerve cells are not essential to the spontaneous, rhythmic contractions of mammalian heart muscle. The probability that nerve cells in the heart are not concerned in the production of the normal contraction will then be too great to be overborne by any facts now in our possession.

Certainly the negative results of Bernstein's experiment will be then no longer of importance. The value of this experiment has indeed been much exaggerated. No part of the heart can be expected to continue its contractions long after its nutrition is cut off. The whole force of Bernstein's experiment lies, therefore, in the tacit assumption that the nutrition of the apex is still maintained. But this is a mere assumption. That the complex system of branching passages which supplies the tissues of the frog's ventricle with blood is

sufficiently open in Bernstein's separated apex is neither certain nor probable. On the contrary, the ease with which the apex of the mammalian heart is kept beating when properly supplied with blood suggests that the nutrition in Bernstein's batrachian apex could not have been properly maintained. We may therefore leave Bernstein's negative results and pass to the questions now before us: Does the apex really contain no nerve cells? and can the apex be made to give spontaneous, long-continued, rhythmic contractions?

It has already been said that the belief in the absence of nerve cells from the apex is well nigh universal. There is, in fact, but one dissenting voice—Berkley (15), in a preliminary communication to the *Anatomischer Anzeiger*, announces that nerve cells are to be found in all parts of the mammalian ventricle. Careful perusal of Berkley's subsequent and fuller account in the *Johns Hopkins Hospital Reports* shows, however, that this is on the whole a somewhat tentative statement.

Concerning the method employed in his investigations, Berkley writes as follows: "Our researches on *mus* led us to discard almost entirely the rapid Golgi method, but a few preparations being made for control specimens; as the picric acid prefixation not only furnished much better stained preparations of the nerves and cell-like bodies, but also gave us sections with but a trifling amount of precipitate, and the muscular structure quite transparent and of a faintly yellowish color, in contrast to the brownish non-transparent preparations, thickly strewn with particles of precipitated chrome silver, of the rapid Golgi method" (p. 83).

Those who have worked with the Golgi method need scarcely be reminded that even a "trifling amount of precipitate" is dangerous, especially in the heart, because of the similarity between many of the precipitated chrome silver particles and the irregular bodies of impregnated nerve cells. The danger of misinterpretation would be formidable, even if the nerve cells were numerous; how much greater must it be in Berkley's preparations, in which it seems nerve cells were rare indeed. "In the ventricle of the mouse," he says, "clean and well-defined nerve cells are met with with infrequency, our best

stained specimens showed two, or even three or four in occasional preparations, but they are never to be found except by accident, or after long-continued search. In one particularly fortunate preparation, we once met three definite cellular bodies not more than 200 μ from the tip of the left ventricle, but such an observation is exceptional" (pp. 90–91). It appears, then, that Berkley used only one of several methods which have been successfully employed for the study of ventricular nerve cells; and that the method which he chose is confessedly not free from suspicion, in that it leaves in the ventricular tissue precipitated particles which might easily have been mistaken for impregnated nerve cells.

Let us turn now to the "nerve cells" of the apex. "Three definite cellular bodies" in "one particularly fortunate preparation" from the ventricle of the mouse were apparently the only apical nerve cells found by Berkley. The search for them in the frog, in the sparrow, and in 120 sections of the dog's ventricle was fruitless.

We have quoted at some length from the parts of Berkley's paper which deal with nerve cells in the ventricle, to show that Berkley himself has no great confidence in their presence. In one place, indeed, he speaks of them as "questionable nerve cells" (p. 97). This hesitation, we presume, explains the omission from the summary of conclusions of all mention of nerve cells in the apex, although the importance of this question is recognized on another page.

Regarding the presence of nerve cells in the apex, we have, in short, on the one hand the testimony of many observers whose various methods have revealed nerve cells without difficulty in the basal part of the ventricle, but have failed utterly to show them in the apex of the same organ; and on the other, the statement of a single observer, who says that nerve cells are never to be found in the ventricle "except by accident or after long-continued search," and who, working with a method which confessedly gives precipitates often similar in form to the bodies of impregnated nerve cells, once saw "three definite cellular bodies" near the tip of the left ventricle. Even if the bodies seen by Berkley were nerve cells, their presence in one section out of many hundred examined by him in his painstaking and laborious investiga-

tion would not prove them to be normally present. A certain amount of variation is to be expected in the heart, as in other tissues; and it may well be that in an occasional heart the nerve cells will wander farther into the ventricle than is normally the case. Such exceptions would prove nothing but the already sufficiently well-known fact that some hearts are abnormal. For these reasons we cannot accept the observations of Berkley as establishing a reasonable probability of the presence of nerve cells in the apex of the ventricle.

The present state of scientific opinion being overwhelmingly in favor of the freedom of the apex from nerve cells, it is evident that spontaneous, rhythmic, long-continued contractions of this region establish the power of the heart muscle to execute such contractions in the absence of nerve cells.

It may perhaps be said that the experiments described above fail to prove the spontaneous character of the contraction. It may perhaps be urged that the blood with which the apex was fed became changed during its defibrination and filtration, and acted in consequence of that change as an abnormal chemical stimulus to the cardiac muscle, producing thereby rhythmic contractions similar to those called forth by strong saline solutions and other chemical excitants. I shall not stop to point out the weakness of such an hypothesis—that is evident at a glance, for it is certainly most unlikely that the blood should be so changed in the few minutes which pass between its withdrawal from the vessels and the establishment of the artificial circulation through the isolated apex. I shall content myself with furnishing a new and, I believe, conclusive proof that the apical contractions are truly spontaneous.

On April 21, 1897, a dog weighing 45 pounds received hypodermatically 0.06 gramme of morphia sulphate, and was completely anaesthetized with ether. Tracheotomy was then done, and the heart exposed by resecting the five upper ribs on the left side. The pericardium was opened and stitched on either side to the margin of the thoracic wound. The second chief branch of the ramus descendens in the apical region on the anterior surface of the ventricle was now freed from its bed for several millimetres, beginning close to its origin

from the main stem of the descendens. An oval piece of the ventricular wall supplied by this branch was then separated from the remainder of the ventricle in such a way that every trace of muscular connection between the two was lost. The isolated piece remained in connection with the ventricle only by a strip of pericardium several millimetres long, which supported the artery and its accompanying veins and was absolutely free of muscular tissue. A good supply of

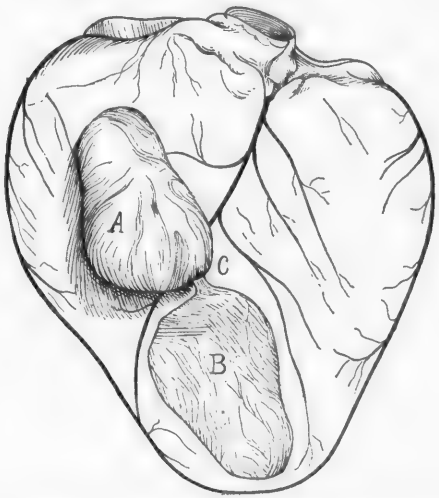


FIG. 2.—From a photograph of the heart of the dog of April 21, 1897. The isolated piece of the apex of the left ventricle gave long-continued, spontaneous, rhythmic, co-ordinated contractions. *A*, under surface of isolated piece; *B*, surface from which *A* was removed; *C*, bridge of pericardium conveying nutrient artery to *A*.

blood was maintained through the artery. The piece thus isolated was 25 mm. long, 15 mm. broad, and 4 mm. thick at its thickest portion. The left ventricle measured, from the origin of the ramus descendens to the apex, 75 mm.; from the origin of the descendens to the isolated end of the basal piece, 50 mm. Hence the latter was cut from "the ganglion free apex" (Fig. 2).

On tying a thread to the end of the isolated piece and lifting it into the air so that it did not touch the ventricle, it appeared to be

contracting, but its movements could not be observed to advantage, because of the impulse imparted to it by the contractions of the ventricle pulling on the vessels which connected the piece to the ventricle. The vagus was therefore stimulated strongly enough to nearly stop the ventricle, allowing but an occasional beat. The isolated piece could then be seen contracting with a slow but perfect rhythm, different from that of the ventricle. The occasional beat of the ventricle was not accompanied by a contraction of the isolated piece. After demonstrating the rhythmical contraction to several persons, the experiment was broken off, having been successfully carried on during more than half an hour.

The contractions observed in the isolated piece could hardly have been excited by changes of pressure in the coronary vessels. It is well known that the pressure in the coronary vessels falls greatly when the heart is arrested by vagus stimulation. The occasional strong contractions of the ventricle, during its incomplete inhibition, raise the pressure considerably; but these wide and sudden variations had in this experiment no apparent effect, the beat of the isolated piece not being synchronous with that of the ventricle. The contractions of the isolated piece of the apex observed in this experiment could not have been caused by the current of action of the ventricle; the piece was raised in the air, and thus kept from touching the ventricle. The action current could not have passed over the vascular bridge and thus excited the isolated piece, because the contractions of the ventricle and the isolated piece were not synchronous. The same total asynchronism is evidence that the beat of the isolated piece was not produced by the alleged impulses discharged by nerve cells in the basal portion of the ventricle passing to the piece over nerve fibres accompanying the nutrient vessels. Still less can the beating of the isolated piece be ascribed to changes in the character of the blood supply; the blood which it received was the same normal blood which was sent to the rest of the heart muscle. The conclusion that these long-continued, co-ordinated contractions were indeed spontaneous is unavoidable.

The apex of the mammalian heart does, therefore, possess spontaneous rhythmic contractility.

SUMMARY.

1. The cause of the rhythmic contraction of the ventricle lies within the ventricle itself.

2. The cause of the rhythmic contraction is not a single, localized, co-ordination centre; the co-ordination mechanism, whatever it may be, is present in all parts of the ventricle.

3. The integrity of the whole ventricle is not essential to the co-ordinated contractions of a part of the ventricle.

4. The apex of the mammalian heart possesses spontaneous, rhythmic contractility.

5. Assuming that the general belief in the absence of nerve cells from the apical part of the ventricle is correct, these experiments demonstrate that nerve cells are not essential to spontaneous, long-continued, co-ordinated contractions of the ventricle.

NOTES AND REFERENCES.

1. Porter.—*Arch. f. d. ges. Physiol.*, lv, 1893, p. 366.

2. For instances of this view, see Kronecker und Schmey, *Sitzungsber. d. Berliner Acad.*, 1884, p. 87; Sée et Gley, *Comptes rendus*, civ, 1887, p. 827; Kaiser, *Ztschr. f. Biologie*, xxx, 1894, p. 279.

3. Kolster.—*Skand. Arch. f. Physiol.*, iv, 1893, p. 14. K. finds that twenty-four hours after infarction the muscle fibres will no longer stain.

4. All the animals used in these experiments were fully anaesthetized with ether or with morphia and ether.

5. Wooldridge.—*Arch. f. Physiol.*, 1883, p. 522; Tigerstedt, *ibid.*, 1884, p. 501. Wooldridge's ligature has also been used by Krehl and Romberg, *Arch. f. exper. Path. u. Pharmakol.*, xxx, 1892, p. 51; and by MacWilliam, *Journ. of Physiol.*, viii, 1887, p. 297. Bohr and Henriques, *Skand. Arch. f. Physiol.*, v. 1895, p. 233, circulated defibrinated blood through a cannula in the left coronary artery of the calf's heart, in order to measure the volume of the coronary circulation. The auricles were of course not removed, and the two hearts employed were kept beating but a few moments.

6. Tigerstedt.—Die Physiologie des Kreislaufs, p. 217.

7. The very extensive literature of this subject has been so often summarized that it is unnecessary to give extended references here. Tigerstedt's Die Physiologie des Kreislaufs contains a sufficiently full account.

Engelmann has recently published in the *Arch. f. d. ges. Physiol.*, lxv, 1896, p. 535, a one-sided review of this literature.

8. Foster and Dew-Smith.—*Proc. Roy. Soc. Lond.*, xxiii, 1875, p. 320.

9. Wagner.—*Neurolog. Unters.*, 1854, p. 227; also Schenck, 1867, His, Jr., 1893, and Pickering, 1893.

10. Engelmann.—*Arch. f. d. ges. Physiol.*, lxv, 1896, p. 119.

11. Dogiel.—*Arch. f. mikr. Anat.*, xliii, p. 223.

12. Bernstein.—*Cbl. f. d. med. Wiss.*, 1876, p. 386; also Bowditch, 1878; and Aubert, 1881.

13. Biedermann.—*Sitz.-Ber. d. Kais. Akad. zu Wien, Math.-phys. Cl.*, lxxxii, 3. Abth., 1880, p. 259.

14. The explanations of the action of muscarin are as yet so hypothetical that it seemed unnecessary to discuss them here.

15. Berkley.—*Anat. Anzeiger*, ix, 1893, p. 33; and *Johns Hopkins Hosp. Rep.*, iv, 1894-5, p. 248.

A STUDY OF METABOLISM DURING FASTING IN HYPNOTIC SLEEP.

By C. F. HOOVER, M. D., and TORALD SOLLMANN, M. D., Cleveland.

Plates XXXIII and XXXIV.

Frank Sohn, on whom the following observations were made, was a hypnotic subject of Mr. Santanelli, a professional hypnotist.

The boy had become so subjective that Mr. Santanelli proposed to keep him in a continuous hypnotic sleep for a week, without food or drink, and to use the seven-days sleeper as an additional attraction for his nightly exhibitions of hypnotism.

Only two days before the exhibition began, Mr. Santanelli called on us and proposed to leave the sleeping subject in our care, and to allow us to make any observations we might choose. The time was too short to make any preparations for observing the loss of water and carbonic acid from the lungs, so we had to content ourselves with analyses of the urine, and making hourly observations of the pulse, respiration and temperature, and daily records of the loss in weight.

Twelve of the students of the Western Reserve Medical School very kindly volunteered to watch the sleeper. The watches were divided into four hours each, two men being on duty together. The patient was so carefully guarded that it would have been impossible to have given him food or drink, or to have practiced any deception regarding the sleep.

Mr. Santanelli claimed that only two weeks previous to coming to Cleveland he had kept another subject asleep for one week without food or drink, and he proposed to do the same in this case; but, as will be seen later, the hypnotist was disappointed.

The subject was 19 years of age, 5 feet 10 inches in height, and weighed 129 pounds; hair, dark brown; eyes, grey; features quite regular, with the exception of a short chin; muscular development

good; panniculus adiposus small in amount; the intelligence rather below that of the average boy at nineteen.

Physical examination revealed no pathological signs in the thoracic or abdominal organs, with the exception of an inguinal hernia, which could be readily reduced and which caused the boy no annoyance. Examination of the nervous system revealed only loss of the conjunctival reflex and diminution of the pharyngeal reflex.

Sohn had been feasting during the preceding week in anticipation of his fast. The urine for the 24 hours preceding the commencement of his sleep was saved, beginning at 7 P. M., July 14. The last urine passed voluntarily was at 7.30 P. M., July 15.

At the conclusion of the evening's performance at 10 P. M., July 15, Mr. Santanelli threw the subject into a hypnotic sleep, telling him that he would not suffer from hunger or thirst nor would he have any desire to pass urine or stool, and that he should remain asleep until the following Monday evening.

At 7.30 P. M., July 16, a catheter was passed into the bladder and 570 cc. of urine were drawn off. At the command of Santanelli the boy made his body rigid, so that he could be lifted from his couch and laid crosswise on the platform of a grocer's scales to be weighed. This same procedure was repeated every evening as nearly as possible at the same hour.

Sohn remained in a quiet sleep without water to drink from 10 P. M., July 15, until 3 A. M., July 17, when he arose from his couch, walked across the room to a water tank and drank three cups of water, amounting to about 700 cc. He immediately returned to his couch. Mr. Santanelli was sent for and the hypnotic sleep renewed. During the remaining time, up to 10 P. M., July 23, the boy remained (so far as we were able to determine) in a hypnotic sleep. From July 17, however, we adopted the plan of giving him a known quantity of water to drink whenever (at the suggestion of Mr. Santanelli to the subject) it was desired.

The pulse, respiration and temperature were recorded every hour during the entire sleep. The temperature was taken in the axilla.

The exact daily loss in weight is not reliable, because on two

occasions the subject was given a pint of water to drink shortly before the evening weighing. For this reason we give only the total loss for the eight days.

At the command of Mr. Santanelli, the rate of the heart-beat was reduced and maintained an average low rate during the entire eight days, with the exception of the time on the morning of the 17th during which the boy was awake.

On the evening of July 23, during the performance, the pulse rate rose gradually, the subject becoming somewhat restless. At the conclusion of the evening performance the subject was directed to walk to the stage, where he was awakened. A sudden rise in the pulse rate occurred at the time of the awakening. From this time on Sohn was beyond our control, so that further observations could not be made on him.

The chlorine was estimated by Mohr's method; the phosphates as P_2O_5 by titration against uranium as described by Neubauer. The total nitrogen was estimated by the Kjeldahl method. The urea was estimated by decomposing with hypobromite of sodium and measuring the resulting nitrogen over the water, making barometric and thermometric corrections.

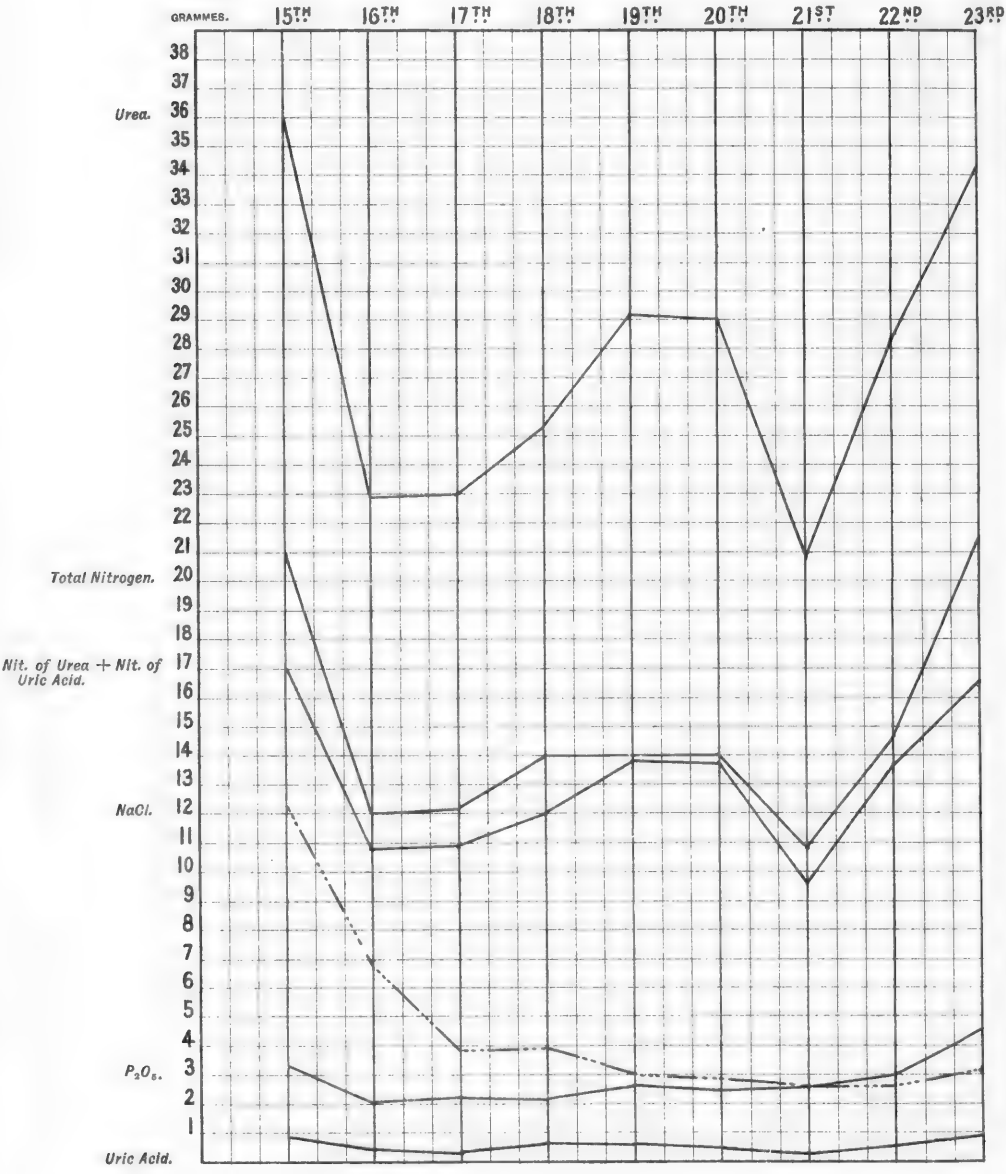
The nitrogen of urea was measured in the following manner: The hypobromite of sodium was freshly prepared for each determination by adding about 1.5 cc. of bromine to 20 cc. of a strong solution of sodium hydrate. This was placed in a "salt-neck" bottle of about 60 cc. capacity. 1 cc. of urine was placed in a short tube (closed at one end) that would rest in a diagonal position within the bottle, thus preventing the urine and hypobromite of sodium from coming in contact and at the same time allowing the bottle to be tightly corked. Through a tightly fitting rubber cork, two glass tubes were passed fitted with others made of rubber. The one opening into the air of the room was closed by a pinch-cock; the other was connected with an inverted burette, which was immersed in the water contained in a litre graduate. After the tube containing the urine had been placed in the bottle and the cork placed firmly in position, the pinch-cock was released so as to equalize the pressure within the burette and the

graduate. The pinch-cock was then again closed. The urine and hypobromite were mixed thoroughly until no more gas was given off. After the apparatus had been allowed to stand half an hour to cool, the burette was elevated so that the water within it and the graduate stood at the same level; in this way the volume of the resulting nitrogen could be measured. By making thermometric and barometric corrections the weight of the nitrogen was determined, and from this known weight the amount of urea was estimated. The method is not a very accurate one, as we later tested it with a known quantity of urea in distilled water and found that the results varied from 10 to 15 per cent. Our Kjeldahl apparatus, however, gave very accurate results with a known solution of urea.

The uric acid was determined by the process known as Hopkins' method, which can be found described in Purdy's book on urinary analysis. This method in brief consists in precipitating the uric acid (in 100 cc. of urine) as ammonium urate, by saturating the urine with ammonium chloride and allowing it to stand from 12 to 24 hours. The precipitate is washed with a saturated solution of ammonium chloride dissolved in 100 cc. of water; 10 per cent of hydrochloric acid having been added, the liquid is allowed to stand at least 12 hours; the uric acid thus precipitated is gathered on a filter and washed with a few cubic centimetres of cold water; it is then dissolved with hot water and sodium carbonate, and water is added to make up 100 cc. The addition to this of 20 cc. of concentrated sulphuric acid raises the temperature just about to the boiling point, and the solution is then titrated against a $\frac{N}{20}$ solution of permanganate of potassium. The only nitrogenous compound present is presumed to be uric acid, so that every cubic centimetre of the permanganate solution used is equal to 0.00375 gramme of uric acid. This procedure in our hands in former experiments had been found to give more constant results and to require less time than the Ludwig-Salkowski method, which is more commonly used. In every instance duplicate determinations of the urine were made.

CHART I

Showing the Elimination in Grammes of Urea, Total Nitrogen, Nitrogen of Urea and of Uric Acid, Sodium Chloride, Phosphates and Uric Acid.



Showing the Hourly Records of Temperature, Pulse and Respiration in the case of Sohn.

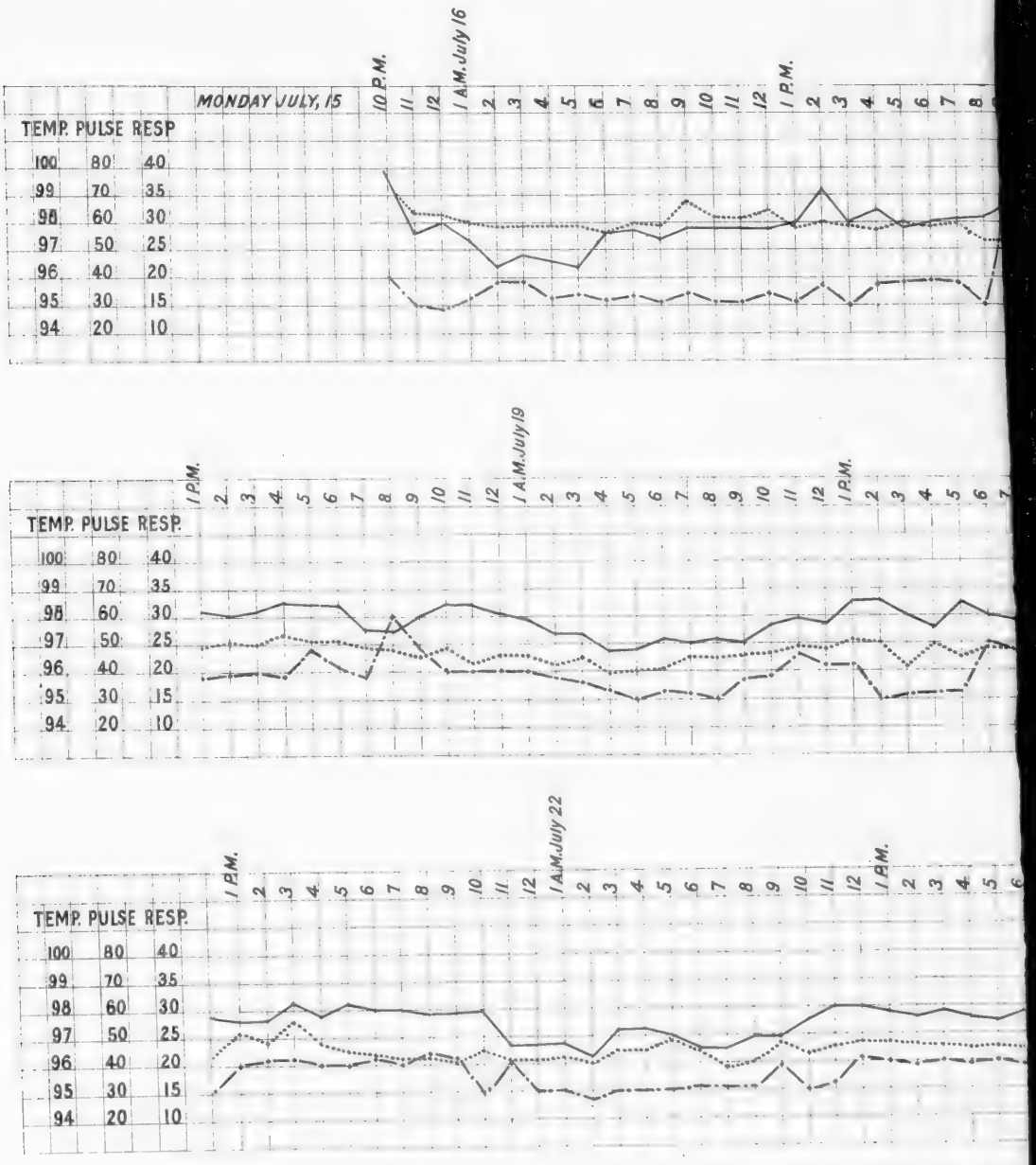


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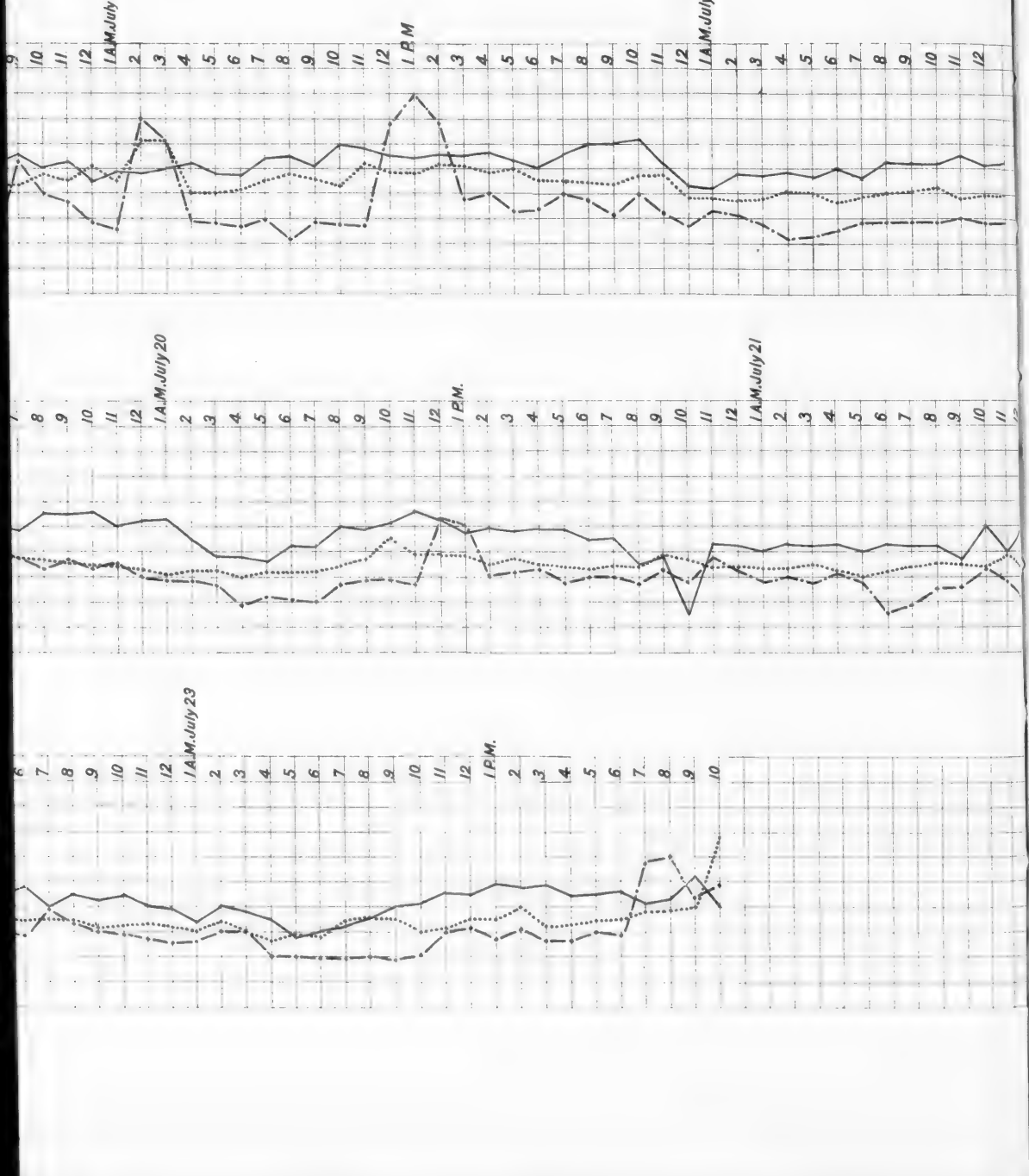
CHART II.

The unbroken line is the temperature, the dotted line is the pulse, and the broken line is the respiration.



The following table gives the results of our analyses of the urine in the case of Sohn.

ANALYSIS OF URINE.

Day of Month	15th.	16th.	17th.	18th.	19th & 20th.	21st.	22nd.	23rd.
Quantity	1350	570	470	530	1020	410	560	820
Reaction	acid.	acid.	acid.	acid.	acid.	acid.	acid.	acid.
Sp. Gr.	1028	1033	1035	1034	1037	1035	1033	1032
Urea	36.21	22.62	22.99	25.24	58.179	20.67	28.26	34.13
Uric Acid	0.824	0.617	0.450	0.538	0.866	0.375	0.572	0.908
P_2O_5	3.381	2.303	2.268	2.270	5.052	2.434	3.150	4.442
Na Cl	12.330	6.837	3.863	3.964	5.954	2.496	2.419	3.296
Albumin	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
Sugar	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
Sediment	....	uric ac.	....	uric ac.	....	uric ac.	uric ac.	uric ac.
Total Nitrogen	20.978	12.369	12.370	14.013	27.988	10.791	14.504	21.582
Nit. Urea	16.875	10.545	10.716	11.766	27.149	9.685	13.272	15.908
Nit. Uric Acid	0.275	0.206	0.150	0.179	0.288	0.125	0.191	0.303
Nit. $\dot{u}+\bar{u}$	17.150	10.751	10.866	11.945	27.437	9.760	13.463	16.211
Differential Nitrogen.	3.828	1.618	1.504	2.068	0.551	1.031	1.041	5.371
Water taken in cc.	....	....	750	750	1150	875	1250	750

Loss in body weight from July 15 to 23 = 5896 grammes.

Loss of nitrogen = 113,617 grammes.

Nitrogen lost, estimated in albumin = 710 grammes.

Nitrogen lost, estimated in muscle = 3341 grammes.

From this table we have plotted the accompanying Chart I (Plate XXXIII), showing by graphic curves the elimination of urea, total nitrogen, nitrogen of urea, and that of uric acid, sodium chloride, phosphates and uric acid.

On Chart II (Plate XXXIV) are the curves of the temperature, pulse and respiration, according to the hourly records.

In the case of Cetti, the Berlin faster, whose urine was analyzed by Munk, and that of Succi, on whom observations were made by Luciani, the uric acid was not determined.

In comparing the elimination of nitrogen in the three cases, it is seen that this was not subject to such variations in the cases of either Succi or Cetti (who remained awake or slept at will and drank water ad libitum) as in the case of Sohn, who was asleep all of the time and took a relatively constant quantity of water.

Nitrogen in the case of Cetti (eliminated in 24 hours urine).

Last eating day		13.49	grms.
1st fasting	"	13.54	"
2nd "	"	12.58	"
3rd "	"	13.12	"
4th "	"	12.39	"
5th "	"	10.69	"
6th "	"	10.1	"
7th "	"	10.88	"
8th "	"	8,903	"
9th "	"	10.83	"
10th "	"	9.46	"

Nitrogen in the case of Succi (eliminated in 24 hours urine).

Last eating day		16.23	grms.
1st fasting	"	13.80	"
2nd "	"	11.02	"
3rd "	"	13.85	"
4th "	"	12.80	"
5th "	"	12.83	"
6th "	"	10.12	"
7th "	"	9.37	"
8th "	"	8.42	"
9th "	"	7.78	"
10th "	"	6.75	"

The loss of body weight was 6350 grammes for 10 days in the case of Cetti; 5700 grammes for 10 days in the case of Succi; 5896 grammes for 8 days in the case of Sohn.

Cetti was a thin man and drank a large amount of water the first few days of his fast. Succi was a better nourished man but drank only a moderate amount of water. The exact amount is not known in either case. It was estimated that Cetti drank 12 litres during the 10 days.

In the case of Sohn it is impossible from the comparatively short

duration of the fast to drawn any conclusions as to the possible relations between the amount of water drunk and the elimination of nitrogen.

As in the case of Succi, so also in that of Sohn, the P_2O_5 elimination became larger in proportion to the amount of nitrogen. There is here of course no relation between cerebral activity and loss of phosphates.

The uric acid fell the first day of the fast in the case of Sohn, but gradually rose the last 24 hours to an amount greater than that excreted on the 15th when he ate a large amount of meat.

The chlorides gradually fell in amount, reaching the minimum on the last day.

The total loss of body weight was 5896 grammes, 3341 of which must have been proteid material, as estimated in lean muscle from the amount of nitrogen lost. Assuming that the maximum amount of glycogen in the liver was 200 grammes, which we may assume was all consumed, the loss in fat and water would be 2355 grammes.

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ON THE OCCURRENCE OF THE FAT-SPLITTING FERMENT IN PERITONEAL FAT NECROSES AND THE HISTOLOGY OF THESE LESIONS.

By SIMON FLEXNER, M. D.

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

The relation which exists between certain diseases of the pancreas and fat-necrosis has been emphasized especially by Fitz in his comprehensive studies of pancreatitis. According to this author* disseminated fat-necrosis in the abdominal cavity is comparatively infrequent in the suppurative form of pancreatitis, while it is relatively common in the hæmorrhagic and the gangrenous varieties. Balser,† who first directed especial attention to this condition, of which he gave a full description, found it in 5 out of 25 autopsies either within the interacinous tissues of the pancreas or in the adjacent or distant adipose tissues. Since this time, fat-necrosis has been observed by a large number of pathologists in cases in which gross disease of the pancreas has been wanting at autopsy. In these instances the necroses are limited, as a rule, to the immediate neighborhood of the gland, although at other times they have been found more widely disseminated when such disease of the pancreas existed. Still more recently, and now that acute suppurative or necrotic pancreatitis has become a field for surgical interference, the condition has been encountered at the operating table.

The coincidence of disease of the pancreas with the occurrence of fat-necrosis in the peritoneum on the one hand and the proximity of the necrotic areas to the pancreas on the other hand lent support to the view, quite early advanced, that a relation of cause and effect must exist between the gland and this pathological process. The first attempt, which may be regarded as at all successful, to prove this

* Acute Pancreatitis. The Middleton-Goldsmith Lecture, 1889.

† Virchow's *Archiv*, xc, 520, 1882.

assumption by experimental means was made by Langerhans.* In his studies† of the histology of the lesions he had satisfied himself that a decomposition of the fat-molecule had taken place, liberating the fatty acids which, after a time, combined with calcium to form insoluble lime soaps. He therefore experimented by injecting sterile pulp of the fresh pancreas into the perirenal tissues of a rabbit with the result of setting up an inflammatory process in which evidences of fat-necrosis were detected. In his repetitions of this procedure he did not always obtain similar results, but although he could claim only a single successful experiment out of twelve attempts, he nevertheless felt justified in considering that "the fat-splitting ferment by acting directly upon the tissues sets up a suppurative inflammation, while its less intense action brings about a decomposition of the oil drops within the fat cells resulting in fat-necrosis."

The experiments which have followed those of Langerhans have consisted in the introduction of portions of fresh pancreas into the peritoneal cavity of rabbits and dogs, the isolation of the pancreas from its main veins so as to bring about the production of passive congestion, thus favoring, as it is thought, the passage of the secretion into the blood, and the separation of one-third to one-half of the head of the pancreas from the tail, which is then permitted to pour its secretion directly into the peritoneal cavity. These experiments, which have been more or less successful, have been made by Dettmer,‡ Hildebrand,§ Körte‖ and Williams.¶ The facts which they established are: (1) The secretion of the pancreas may enter the peritoneal cavity without setting up diffuse inflammation, a conclusion previously arrived at by Senn; (2) in a certain number of instances the free, sterile pancreas or the pancreatic secretion causes focal fat-necrosis;

* Experimenteller Beitrag zur Fettgewebsnekrose, Virchow's Festschrift, 1891.

† Virchow's *Archiv*, cxxii, 252, 1890.

‡ Experimenteller Beitrag zur Lehre von den bei Pancreatitis haemorrhagica beobachteten Fettgewebsnekrosen und Blutungen, Inaug. Diss. Göttingen, 1895.

§ Ueber Experimente am Pankreas zur Erzeugung von Fettnekrosen, *Centralbl. f. Chirurgie*, xxii, 297, 1895.

‖ *Berliner Klinik*, 1896, Heft 102.

¶ *Boston Medical and Surgical Journal*, 1897, I.

and (3) the element of infection plays an insignificant, if not an entirely unessential, part.

In order to connect more certainly the pathogenic action of the pancreatic secretion with the fat-splitting ferment, and in view of the fact that this ferment itself is not obtainable in a form suitable for experiment, the effects of trypsin were tried. It was found, especially by Dettmer,* that pure trypsin caused a sero-hæmorrhagic exudation into the peritoneal cavity, but was without power to set up fat-necrosis. The diastatic ferment having already been excluded, it was regarded as highly probable that the fat-splitting ferment was the active agent.

My present studies have dealt with two problems. The first was the demonstration of the presence of the fat-splitting ferment in the areas of necrosis and its absence from the normal fat in a suitable human case. The second was to confirm this observation by making similar tests upon animals in which fat-necrosis had been experimentally produced. In the second series of cases experiments were made with a view of determining how long the ferment remained in the tissues in demonstrable conditions or amounts.

I may say in this place that the successful experimental lesions were subjected to microscopical study and the existence of necrosis was proven. The histology of the experimental lesions is also considered in this communication.

The method which was uniformly followed in the demonstration of the ferment is essentially that of Claude Bernard, for the details and practical carrying out of which I am indebted to Dr. Abel, to whom I wish to express my obligations. It consists in preparing a perfectly neutral fat, which I did from fresh butter by dissolving it in ether, adding a few drops of NaOH and washing out with successive quantities of distilled water. The separated ethereal solution of neutral butter was evaporated over a water bath and the tests were made at once. For this purpose, in each instance, I employed (1) a piece of the pancreas itself, (2) one or more focal necroses, and (3) a piece of adipose tissue equal in size to the pancreas or necroses, this piece

* Op. cit.

being taken at a distance from the latter. The pieces of tissue were placed in 90 per cent pure alcohol for from one-half to two hours, pressed in filter paper, reimmersed in the alcohol for a short period, again pressed and then allowed to become air-dry. They were then cut into morsels, which were incorporated with the neutral fat in watch-glasses which were then covered and placed in the thermostat at the body temperature.

For the demonstration of the action of the ferment two methods were employed. The first was the detection of the liberated fatty acids by the sense of smell. The second consisted in dissolving the butter, etc., in pure absolute alcohol and adding tincture of litmus to the alcoholic solution. It was quite remarkable how well the two tests agreed with each other. The exact details will be given in the individual protocols.

It would seem that the reaction takes place quickly if the ferment is present in an active condition. In not a few instances a distinct and even marked reaction was obtained within six minutes from the time of placing the watch-crystals in the thermostat.

The animals used for experiments were cats and dogs. The former appeared to be better adapted for the purpose. The operations consisted of (1) ligation of all the veins proceeding from the pancreas, which was quickly followed by a vivid congestion of the gland, and the laceration of the organ by means of a sharp hook; (2) the same operation, in addition to which a strong ligature was thrown about the splenic half of the organ; (3) ligation of the veins, tying off of the splenic half, and section beyond the ligature; (4) the isolation of the duct of Wirsung, its ligation where it entered the duodenum and section. The effects of congestion alone were tried in two cases without marked success.

The object in these experiments was to produce necrosis at a distance from the gland which would serve for the tests mentioned. It was also considered desirable to avoid all infection of the peritoneal cavity. The most satisfactory results were obtained after ligating the veins and lacerating the pancreas. Tying off one-half of the organ was soon abandoned, inasmuch as it was found that the ligated part

sometimes suppurated and the necroses were not more extensive than in other cases. Cutting the duct of Wirsung (one case) did not lead to extensive necroses. The focal areas were found in the pancreas and mesenteric fat close to the site of operation and were small in size. The duct in the cat is hardly larger than a capillary tube and, it is believed, quickly becomes obliterated after section. By the use of rigid surgical precautions, except in two cases of suppuration about the ligature around the pancreas, in one instance only (a dog) was a general peritonitis encountered. Notwithstanding a sero-purulent exudate in the abdominal cavity, this animal appeared to be in perfect health when killed 3 days after the operation.

The necroses varied in extent. They were always to be detected about the pancreas in the interacinous and peripancreatic adipose tissue. They were usually present in the fat of the gastrohepatic omentum and more variably in the great omentum and mesenteric fat. When in the mesentery the necroses were likely to be in the duodenal and upper jejunal portions and in that of the descending colon. They were never discovered in the perirenal tissue. Wherever adhesion took place between the omentum and the lacerations on the surface of the pancreas, there fat-necroses were always found. In size the necroses varied from a pin's head or less to a pea. The smaller ones were yellow or white and opaque, the larger often hæmorrhagic. The latter were usually selected for the tests.

With one exception all the animals were killed, chloroform being used for this purpose. The animal which succumbed spontaneously was a full-grown but rather poorly nourished cat, which died two days after the operation. There were in this instance many areas of necrosis in the pancreas and mesentery and fewer in the omentum. In part they were hæmorrhagic. The other animals were killed on the 2nd, 3rd, 4th, 6th and 8th days respectively. Positive reactions for the ferment were obtained in all except the two longest periods mentioned.

In order to determine whether in the long periods the ferments were present at an earlier date only to disappear later on, the animals were subjected to a second operation (Protocols C, D and E), at which

time necrotic foci were excised and tested, the peritoneal cavity being again closed. These tests were made on the 3rd day after the first operation. The cats were killed on the 6th and 8th days respectively. The first tests were positive; the second negative in all instances.

When we come to consider the histology of the experimental lesions we shall find that a great difference exists in those of the first three and those of the 6th and 8th days. While in the former the process is very acute, in the others the evidences of cicatrization are most pronounced.

The conclusions which may be drawn from the foregoing observations are: (1) In peritoneal fat-necrosis the fat-splitting ferment is demonstrable at certain stages of the pathological process; (2) it is present in greatest amount in the early stages and may disappear in the later ones when healing is well advanced; (3) although it cannot be affirmed that steapsin is the direct cause of the necrosis of tissue, such an assumption is rendered highly probable by its constant occurrence in the diseased areas, its absence from the healthy fat, and the nature of the pathological changes; (4) the escape of the pancreatic secretion into the peri- and para-pancreatic tissues is the origin of the necroses, and this escape is facilitated chiefly by lesions of the pancreas itself, but also by disturbances in its circulation.

That necrosis of fat cells may result from other causes is certainly not excluded by these findings. The genesis of similar lesions found in the marrow of the bones by Ponfick* in the subcutaneous fat (Chiari) and pericardial fat (Balser, Chiari) is not immediately apparent. That micro-organisms may, in these cases, play a part is, in my opinion, very probable indeed. Ponfick's case was one of empyema in which, besides the lesions in the medulla of the bones, areas of softening, not due to vascular occlusion, existed in the myocardium.

The histology of the fat-necroses, as it occurs in human beings, has been studied by Ponfick, Balser, Fitz, Chiari,† and especially by Langerhans.‡ The experimental lesions also have been subjected to

* Virchow's *Archiv*, lvi, 541, 1872.
† *Prager Medicinische Wochenschrift*, viii, 1883.
‡ Virchow's *Archiv*, cxxii, 252, 1890.

microscopical examination and compared with those found in man. The main facts to be gleaned from these observations are as follows: The pathological process begins with a decomposition of the neutral fat contained within the fat cells; the fluid constituents are eliminated and the solid fatty-acid crystals remain behind. These, after a time, unite with calcium to form insoluble lime salts. The pathological products are found within the protoplasm of cells whose nuclei have already lost or are preparing to lose their affinity for staining agents. The general form and characters of the cells are retained for a time; but in later stages the lime compounds occur free under the form of granules, rings and hyaline masses (Schollen), which as a whole appear white and non-transparent. Thus it happens that a small number of cells, a whole lobule of adipose tissue or even several adjacent lobules may give rise to a necrotic focus which now becomes the seat of a reactive (demarcating?) inflammation.

Pathological alterations within the blood-vessels may be slight or entirely wanting, and are, at best, so inconstant and variable as to be excluded as representing the exciting cause of the lesions. In the same way the part played by micro-organisms can be only an insignificant one and is probably limited to an occasional instance. At any rate all evidences of constancy of relationship between bacteria and the necrotic foci are thus far wanting.

One of the objects of my study of the histology of the experimental lesions was to compare them with those occurring in the course of disease in man. As a basis for this comparison two human cases were studied, in one of which the necrotic lesions were widely disseminated (Protocol A) and in the other were nearly limited to the pancreas and peripancreatic tissue (Protocol B). In the first case only was the fat-splitting ferment demonstrated in the necroses; in the other no attempt was made to detect it owing to the intimate association of the lesions with the pancreas. Still another purpose of this study was the determination of the changes which take place in the tissues coincidently with the disappearance of the ferment from the necrotic foci. The observations upon this point may be taken as a contribution to our knowledge of the healing of fat-necroses.

There is little difficulty in the human cases mentioned in confirming the results of Langerhans' researches. In addition it is to be noted that lesions may come under observation early, before the lime compounds have formed, in which case besides the changes peculiar to fat-necroses, those of an acute inflammatory nature are also present. This fact is true of one of our cases (Protocol A) in which none of the disseminated foci of necroses had been incrustrated with lime. The white, opaque central mass is composed of confluent cells, derived from the adipose tissue, the individual outlines of which have been lost and in which nuclei either complete or as fragments are entirely wanting, but which are occupied by fatty-acid crystals. The addition of concentrated sulphuric acid and then water does not bring these crystals out more distinctly, but quickly decomposes the fat in the unaltered cells, causing a separation of an abundance of crystalline fatty acids. At the end of twenty-four hours no further change has taken place; sulphate of calcium crystals have entirely failed to make their appearance.

Just outside the completely necrotic focus is a zone of infiltration in which cells and fragments of cells and nuclei are found in large amounts. This presents somewhat heterogeneous characteristics; it constitutes in part the zone of reaction—demarcating inflammation—and encloses many ring-shaped and globular hyaline bodies which are characterized further by their peculiarly intense staining with hæmatoxylin. Among the foreign elements in this mantle, polymorphonuclear leucocytes and cells of the lymphoid type are to be distinguished. Beginning at this point and extending for a variable, but often considerable, distance into the surrounding tissue, there are evidences of an inflammatory invasion consisting of œdema, hæmorrhage and especially of fibrin. Many swollen and necrotic cells (emigrated and tissue elements) are present in this part. It is noticeable that the rich network of fibrin tends to extend along the connective tissue septa, against which many of the necrotic foci abut. The diffusion of the simple inflammatory lesions, in contradistinction to the definitely circumscribed nature of the specific necrotic areas, is a remarkable feature of the pathological process.

Evidences of proliferation of the fixed tissues are abundant; even in such early stages as just described they are discernible; but later (Protocol B) they are much more marked. There is nothing peculiar about the manner of this new growth, except that it is peripheral. The necrotic centres do not become invaded but gradually shrink and finally would appear to be completely replaced by connective tissue. At the time of great activity of the tissues the acute inflammatory process is no longer to be made out; red blood-corpuscles, serum and fibrin have disappeared.

The pancreas itself suffers in two ways; it undergoes necrosis in the same way as the adipose tissue. This is observed on the surface (extension by continuity) and deeper down near the interlobular connective-tissue bands. Again, it is invaded by a new growth of connective tissue not limited strictly to the fields of necrosis. Finally, and in this way, small nodules characteristic of intestinal pancreatitis with loss of parenchyma come to be formed.

The acute lesions of the experimental cases approach very closely to the corresponding lesions in man, while the older ones in animals pass through more typical stages of healing, and apparently also in a shorter period of time. The central masses of necrotic cells are indistinguishable in the two forms, while the peripheral zone of infiltration is perhaps greater in the experimental cases. The elements composing this zone differ somewhat. The great majority of preserved cells exhibit single, deeply-staining nuclei. Fibrin appears somewhat variably; necroses 72 hours old (Protocol C) may be devoid of it, while again it may be abundant in about the same period or even later (Protocol D and E). The pancreas itself may suffer severely or may escape entirely. In the first instances large necroses exist within the parenchyma. The venous radicles are occupied by light fibrinous thrombi.

Cicatrization is already under way on the sixth day (Protocol D), but on the eighth it is well advanced (Protocol C). The new cells are developed at the periphery of the focus of necrosis, the proliferation extending well beyond the immediate site of injury. The necrotic area gradually shrinks, becoming smaller and smaller without being

invaded to any extent either by wandering or fixed cells. Multinuclear (Giant) cells occur either at the most recent edge next the necrosis or at some distance in the adipose tissue. At this time (8th day) the outermost zone of granulation tissue is already fibrillated. If the area has been hæmorrhagic, blood pigment (hæmatoidin) is still present and is enclosed in the new cells.

The central mass of necrosis is not completely calcareous, and it is exceptional to obtain the micro-chemical reaction for calcium.

From the following protocols more detailed information may be obtained.

Protocol A. Woman, aged 50 years. Well nourished; well developed panniculus. Sudden death; symptoms of œdema of the lungs. Anatomical diagnosis: Gall-stones in common duct; dilatation of duct above the concretions; dilatation and distention of gall bladder; jaundice. Disseminated peritoneal fat-necroses. Moderate chronic diffuse nephritis.

The under surface of the omentum shows a considerable number of foci of fat-necrosis, surrounded by hæmorrhagic or hyperæmic zones. The nearer the pancreas is approached the more numerous become these foci. The greatest number in the omental fat are found on the left side, passing down almost to the crest of the ilium. Where the necroses are most abundant near the pancreas, adhesions, easy to break down, exist between this organ and the omentum. Similar adhesions between the omental foci and the abdominal wall, near the iliac crest, are met with, and hæmorrhage has taken place freely into the pouch formed in this manner. The pancreatic interstitial fat especially in the splenic portion and the mesentery also show foci of necrosis. The pancreatic duct is not dilated; its contents are, however, thick and opaque. The lymphatic glands in the neighborhood of the pancreas are swollen and reddened; the general peritoneal glands appear to be normal.

The following tissues were tested, in the manner described, for the fat-splitting ferment: (a) a bit of dog's pancreas, (b) a bit of pancreas from this case (controls), (c) several of the focal necroses with the adipose tissue immediately surrounding them, (d) adipose tissue from a distance. Results: Positive reaction in ten minutes in all except d; more marked reactions at the end of 30 minutes. No development of rancidity in d at the end of the experiments—after one hour.

Cultures made from the viscera after returning to the laboratory (the autopsy having been made at a distance) gave the following results: Heart's blood, liver and gall-stones were negative. Pancreas, spleen and

fat about the pancreas and kidneys gave a bacillus belonging to the group of B. coli communis.

Protocol B. Man, aged 56 years. Heavy periodical drinker. Large, well-developed, obese. Anatomical diagnosis: Biliary (hypertrophic) cirrhosis of liver; ascites; chronic diffuse nephritis; lobular pneumonia; general passive congestion of viscera; multiple foci of fat-necrosis in the pancreas.

The pancreas is large, grey in color and firm in consistence. There exist just beneath the capsule several whitish areas, the largest not exceeding 5 mm. in extent, which proved to be fat-necroses. They are more numerous in the substance of the organ where they appear in the form of lines and squares, and often contain a putty-like material. The addition of H_2SO_4 and water to this material yields, after a time, gypsum crystals. The ferment was not sought in these foci owing to their proximity to the pancreatic tissue.

Protocol C. March 30th, noon, operated upon two cats as follows: No. 1; tied off largest veins only, excepting omental branches; No. 2; tied off all the veins which could be found; lacerated pancreas with a sharp hook. Three days later (April 3, noon), cat No. 1 opened under ether anaesthesia; a number of small, white opaque necroses existed in the omentum near the pancreas; somewhat larger ones present in the pancreas itself. Clean peritoneum. A bit of the fat containing three small necroses (not exceeding 2 mm. each) excised; abdominal cavity closed. Cat No. 2 opened in the same manner. Peritoneum clean; omentum free except at one point, where it is tucked over a laceration in the pancreas. Numerous fat-necroses in the omentum and in the fat about the pancreas; the individual ones are much larger than those in No. 1. Two focal fat-necroses excised; one of these represents one-half of a large omental focus, the other half being left for a future experiment. A single hæmorrhagic node free from visible necrosis also excised from the omentum. Abdominal cavity closed. Tests for the ferment: No. 1 showed no reaction to the sense of smell in one hour; very faint reaction to litmus. Butter control negative. No. 2: the necroses tested separately; hæmorrhagic area also tested. The necroses reacted promptly both by odor and to litmus. Hæmorrhagic nodes gave no reaction. April 8 (8 days after first operation), both animals chloroformed. No. 1: No necroses to be found except in and near the pancreas about the ligature. No. 2: Clean peritoneum; the foci of necrosis fewer in number and reduced in size. A number of small ones (pin-point to pin-head) are found in the omentum. The remaining half of the excised necrosis is reduced to the size of a canary seed and is firm and white. Tests for ferment: (a) one focus 1.5 x 2 mm. from the lesser omentum; (b) a piece of

the great omentum having a number of necroses side by side; (c) the remains of the partly excised necrosis; (d) bit of the pancreas. Results: no reaction either to sense of smell or to litmus in (a), (b) and (c). Positive reaction (5 minutes) in (d).

Protocol D. April 22, 10 A. M., operated as follows: Cat No. 1; veins tied; pancreas lacerated. April 24, 4 P. M. (after 54 hours), peritoneum opened under ether narcosis. A number of focal areas of necrosis in or near the pancreas; other smaller ones at a greater distance. Two nodules excised (a) hæmorrhagic area from the omentum, (b) opaque area from the capsule of the pancreas. Test for ferment: (a) faint reaction of rancidity and to litmus; (b) stronger and marked reactions. April 28 (after 6 days), animal chloroformed. No distinct nodules in the omentum; several flat white areas in the pancreas. No reaction from the former.

No. 2. Smaller, poorly nourished cat. Pancreas lacerated without tying off of veins. Died during night of April 23d. Autopsy, April 24th. Peritoneum clean; the edges of the wound sticky, but no pus found. Many areas of focal necrosis in pancreas, mesentery and omentum. Bacteriological examination of cover-slips from the wound showed a few doubtful cocci; cultures from peritoneal cavity, sterile. Ferment in necroses (two tests) and in pancreas (control).

Protocol E. May 11th, noon, operated on two cats as follows: No. 1. half grown; tied off the veins and lacerated the pancreas. May 13, animal died. No necroses in the omental or mesenteric fat. Several small opaque points near the pancreas. No tests. Cause of death not made out. No. 2. Full grown animal. Tying of veins, laceration of pancreas and ligation of splenic half of the organ. Section of the pancreas beyond the ligature, permitting the splenic half with its ducts to be in free communication with the peritoneal cavity. May 14, noon, under ether anaesthesia opened the abdomen and removed (a) bit of adipose tissue from the omentum; (b) a focus of necrosis from this situation; (c) necrosis in the pancreas; (a) and (b) tested for the ferment. Results: from adipose tissue, no reaction; from necrosis, positive reaction; (c) reserved for histological study. May 17. Cat chloroformed. External wound suppurating; peritoneal cavity clean. A number of small, opaque foci of necrosis in the omentum. Owing to their small size several were united for the test. A piece of pancreas from the animal used as a control. The necroses gave no reaction; the pancreas gave positive results. The largest necrotic area was studied histologically.

Protocol F. Cat; operation March 18. Veins ligated; ligature about splenic portion of pancreas. Chloroformed March 23. The ligature about the pancreas had nearly severed the organ. It was covered with a small quantity of sticky pus-like material. Peritoneum otherwise clean.

Many foci of necrosis, the greatest number being near the pancreas on the splenic side. They involve the omental fat over the stomach and its free portion, the mesentery and the substance of the pancreas. Positive reactions for the ferment from the pancreas and from the necroses from omentum and mesentery. No reaction from adipose tissue alone.

Protocol G. Same operation as and similar results to those in *F*.

Protocol H. April 8, 11 A. M. Full-grown cat. Isolation of the duct of Wirsung at its entrance into the duodenum; ligation at the intestine and section. A small drop of clear fluid immediately escaped from the proximal end. Animal chloroformed April 12, 10 A. M. Peritoneal cavity clean. No general foci of necrosis. On the other hand, necroses exist about the ligature, in the fat between the duodenum and the pancreas, extending along the sheaths of the bile and the blood-vessels towards the liver. Duct dilated. No test for the ferment.

Protocol I. Small black dog. Operation March 16. Ligation of veins, ligation of the splenic half and laceration of the pancreas. Chloroformed March 22. External wound granulating; peritoneum clean. The largest area of necrosis is 6 cm. from the pylorus and extends from the pancreas to the intestines, following the ligated blood-vessels. At the intestine (duodenum) the necrosis spreads in the form of fine lines over the serosa. Similar white lines, showing nodosities, and suggesting strings of beads run over the pancreas itself. Test: (a) fat about kidney free from necrosis; (b) pancreas; (c) fat with lines of necrosis from duodenum. Reaction in from 6 to 8 minutes in (b) and (c). No reaction in (a). The microscopical examination of the white contents of the necroses, which had the consistence of Neufchatel cheese, showed it to be composed of a mass of necrotic and oil-containing cells (compound granular corpuscles) and fatty-acid crystals.

Protocol J. Similar experiment to *I*, except that the pancreas was not ligated. Dog killed on the 7th day. Several necroses near the pancreas. No tests.

Protocol K. Dog; operation March 24, veins tied, laceration of pancreas. Chloroformed March 26. Numerous necroses in omentum and mesentery and about pancreas. Tests positive from pancreas and necrosis (two situations); negative from fat at a distance.

Protocol L. Cat; operation April 15, 10 A. M. Ligation of veins; laceration of pancreas. Chloroformed April 17, 10 A. M. Peritoneum clean. Duodenal end of pancreas swollen and oedematous. The omentum shows several areas of hæmorrhagic infiltration with doubtful evidence of necrosis. What appears to be necrotic fat discovered along the sheaths of the portal vessels. Tests with pancreas, supposed necroses in omentum and fat at a distance certainly free; all failed to react excepting the first.

A CASE OF DOUBLE TERATOMA.

CLINICAL REPORT BY R. W. LOVETT, M. D.
PATHOLOGICAL DESCRIPTION BY W. T. COUNCILMAN, M. D.

PLATE XXXV.

The following case of teratoma of the testicle followed by teratoma of the head is interesting both from a clinical and a pathological point of view.

Clinical history.—The case was first seen by Dr. Lovett in consultation with Dr. John B. Curtis of Somerville on June 6, 1894. At this time the child was nearly three weeks old, having been born on May 18 after a normal pregnancy and labor. The other child in the family was well developed and strong. The patient was normal with the exception of an enlargement of the scrotum, which was noticed at birth. This swelling, in size about as large as a hen's egg, was situated on the right side and had the appearance of a hydrocele. The diagnosis of hydrocele having been made, Dr. Curtis did nothing in the way of treatment until it had become obvious that the tumor was increasing in size. On June 2 an exploratory puncture was made, and a light yellow serous-looking fluid, amounting to about a gramme was obtained and was followed by some blood. When seen by Dr. Lovett on June 6 the child appeared to be a healthy, well-developed boy, normal in every respect save for the scrotal tumor. The scrotum was very much swollen, dense and shiny, the appearance presented being that of an enormous hydrocele. The circumference of the tumor over the middle portion was 8 inches. Aspiration with a hypodermic needle was attempted under the impression that the tumor was a large hydrocele; a gramme of fluid was obtained from a puncture at one point and was immediately followed by blood. In no other place could fluid be obtained by puncture.

A provisional diagnosis of malignant tumor of the testicle was made, and three days later the testis was removed. The very much thickened cord was dissected out as far as the external abdominal ring, where it was tied and cut off. Union took place by first intention, and on June 14, 6 days after the operation, the child was sent home, and on the 28th was dismissed from medical care.

The specimen was examined both in the fresh state and after hardening in Müller's fluid. The outside of the tumor was smooth. On one side of it the epididymis could be distinctly made out. The tumor occupied the position of the testicle. It was oval in shape and measured 7 x 5 cm. On section it was found to consist of a solid stroma, in which appeared small islands of cartilage enclosing numerous cysts of various sizes. The largest of the cysts measured 1 cm. in diameter. The smallest were just visible to the naked eye.

Microscopic sections were made from the tumor in various places. Examination of these shows that the tumor is composed of cysts and solid tissue. In the latter there is a large amount of striated muscular tissue, the fibres not having any definite arrangement. They appear both singly and in masses; though found in all parts of the tumor, they are more abundant in some parts than in others. The muscular fibres themselves are small and contain a relatively greater number of nuclei than normal. No nerves were found in connection with these fibres. Scattered in the tissue are small areas of cartilage, the largest measuring 2 mm. in diameter. Most of the cartilage is hyaline, although in a few of the areas fibrous tissue is found between the cells. Bone is found in various places, both in connection with cartilage and free. It shows the characteristics of newly forming bone. It contains numerous typical bone corpuscles lying in large wide spaces and does not possess a definite system of Haversian canals. A large portion of the bone is covered with osteoblasts; in places there are large multinucleated giant cells lying in depressions in the bone. The soft tissue of the stroma contains a considerable number of round and spindle-shaped cells. In places these are so numerous as to give to the section a distinctly sarcomatous appearance, and in other places there is a considerable amount of fibrous or mucoid tissue between the cells. Cysts are found in great abundance in the tumor; they are all lined with epithelium. In some the wall is smooth; in others there are numerous papillary projections extending into the cavity. The character of the epithelium lining the cysts varies. In some there is a single layer of the low columnar type; in others the epithelium consists of numerous layers and has the characters of skin epithelium with

a well-marked stratum corneum, while in others it partakes more of the character of the epithelium of a mucous membrane. Some of the cysts are lined with a single layer of ciliated epithelium; or the epithelium is ciliated over some and not over other cells. In one cyst the epithelium is ciliated on the surface, while below this there are two or three layers of cylindrical cells, the arrangement being similar to that found in the lining of the trachea and the large bronchi. Most of the epithelium contains a considerable number of dark pigment granules in and between the cells. In one of the sections there is found a structure which closely resembles parts of the eye. At this place there is a flattened cyst which is partly covered with flat cells containing masses of black pigment. On the wall opposite to this pigmented epithelium, and in places in connection with it, there is a formation of epithelium closely resembling the retina. On the surface of this, close to the pigment layer, there is a smooth lining of epithelium with projections not unlike the cones of the retina. Back of this there are two or three layers of oval nuclei similar to those of the granular layer. A diagnosis of teratoma was made.

Clinical history continued.—The patient, who had suffered much pain before the operation, began steadily to improve, and on September 1 was reported as being strong and well in every way.

Early in January the child was brought to Dr. Lovett's office on account of a swelling in the right parietal region, which had been noticed for over a month. The tumor was connected with the skull. The skin was movable over it. It was hard, about the size of half an apricot, and gave the impression of having been pressed through the skull. The head appeared to be distinctly hydrocephalic, being out of proportion to the size of the child.

Dr. Burrell saw the case with Dr. Lovett and a provisional diagnosis of sarcoma of the skull was made, and in the middle of January, 1895, the child was operated upon at the City Hospital. A skin flap having been made and dissected back, a soft tumor containing and partly covered with bone was found attached to the skull. It was detached by means of a periosteal elevator and a sharp scoop, leaving the skull rough and bare under it. The growth was soft and contained spicules of bone. The wound was stitched up. The child suffered a good deal of shock from the loss of blood during the operation, as the tumor was quite vascular.

The tumor was sent to the pathological laboratory and a diagnosis of teratoma was made. The head at this time was watched very carefully and was found to be growing in size. It increased as rapidly as 1 cm. a day in circumference, and the left parietal region was seen to be bulging. Two weeks later at a private hospital a large flap was made, near the site of the former incision, exposing the skull. An opening was made with a 1¼-inch trephine, and at the bottom a large vascular mass containing cysts was found. The hole was extended with rongeur forceps upwards and backwards, and an exploration of the tumor mass was made. The growth was so large in extent that its removal was manifestly impossible, and since it was thought to be a tumor of the brain substance, extensive destruction of it was avoided. The wound was closed and sutured. It united by first intention, and the child seemed somewhat relieved by the operation.

Neither at this nor at any other time in the history of the case was there any tendency toward convulsions nor were there any symptoms indicating implication of the motor area. A fatal prognosis was made, and the child kept under observation from this time on. The circumference of the head continued to increase at about the rate of 2 cm. a week. In March the child began to emaciate rapidly. The skin over the tumor broke and suppuration took place. Toward the end of March there was gangrene of some parts of the skin over the tumor and a fetid discharge from several sinuses. The child became cachectic and at times refused to nurse, almost always suffering extreme pain. Opiates were given in moderation. The child gradually sank and died, April 23, 1895.

Plate XXXV, Fig. 1, is a photograph taken during life. Microscopic examination of the portion of the tumor removed showed numerous cysts, not a few of which were filled with sebaceous matter and hair. Many of the cysts were lined with mucous epithelium and mucous glands were found deep in the tissue. The tumor extended into the button removed by the trephine, but the bone itself appeared to have taken no part in the growth.

The autopsy was made on April 24, 1895.

The body was large for the age of the child; somewhat emaciated, pale and anaemic. On the top of the head, extending more towards the left side, is an enormous tumor mass. The surface of this is irregular; at various places there are knobby projections, the largest being 6 cm. in diameter. Below the tumor the skull was pressed out on the right side.

Over its anterior surface the tumor was covered with skin which was not adherent to it. Posteriorly, the skin in several places was absent over the surface of the tumor. It was everywhere extremely thin and in places necrotic and infiltrated with pus. The necrosis had extended into the tumor. The largest projection of the tumor was over the anterior fontanel; there was also a second of considerable size on the left side at about the middle of the coronal suture. An incision was made completely around the tumor and the skin dissected off from it. The skin was in no place directly adherent to the tumor and was not involved in its growth. Beneath, the tumor was everywhere adherent to the dura. There are no adhesions between the dura and the pia. On removal of the tumor the left side of the brain was found greatly compressed; the convolutions were flattened and the mass of the brain was pressed over to the right side. The projection on the right side of the head was not occupied by the tumor, but by the displaced brain substance. The convolutions, though greatly flattened, were otherwise normal. The weight of the brain was 950 grammes. The pia at the base of the skull was smooth and normal, and the vessels were of normal size. Microscopic examination of the brain after hardening showed no evidence of degeneration.

The tumor weighed 1320 grammes. Its outer surface, especially on the left side, is partly covered with thin bone. In some places the bone is eroded, the tumor protruding through it in round masses. Laterally and anteriorly there are numerous projections apparently composed of cysts with soft fluctuating contents. Long spicules given off from the larger bones extend over the surface. The largest portion of the tumor corresponds in position to the posterior part of the anterior fontanel. A section made directly through it shows that it contains numerous cysts. In places there are small areas of calcification, which lie in dense masses of connective tissue extending in various directions through the tumor. The general appearance of the tumor on section is that of a greyish, soft, medullary mass. The contents of the cysts vary; some are filled with a clear thin fluid, others with a thick, more or less gelatinous material similar to the contents of multilocular ovarian cysts, while in others, again, a brownish material appears. In many of the cysts hairs are found among the contents. In the posterior part of the tumor, corresponding to the areas of necrosis and suppuration, some of the cysts contain almost clear pus. The lower surface of the tumor is covered by the dura and in no place projects below it. The tumor is adherent to the upper surface of the dura and can be separated from it by breaking up the adhesions. Nowhere is there an integral connection between

the dura and the tumor, and nowhere is the skin adherent to the tumor except by accidental adhesions. The bone over the posterior portion of the tumor is in places necrotic and eroded.

The pus in the area of purulent infiltration shows numerous streptococci, and cultures made from the tumor and the organs show the same organism in great abundance.

The remainder of the autopsy showed nothing abnormal with the exception of emaciation.

Plate XXXV, Fig. 2, shows a section through the tumor of the head, about two-thirds of the natural size.

Microscopic examination.—The tumor of the brain was hardened in corrosive sublimate and in formalin. Examination of sections shows the presence of numerous cysts differing in size and lined with various sorts of epithelium. In the solid part of the tumor several varieties of tissue can be made out. The stroma, generally, is rich in cells and in places it has a definitely sarcomatous aspect. There are large numbers of nerves in the tissue. Some of these are arranged in bundles and have the character of medullated fibres. In connection with these nerves, there are groups of ganglion cells in all respects similar to the sympathetic ganglia. In other parts of the tumor a good deal of bone is found, the character of which varies. In places it resembles normal adult bone with corpuscles and Haversian canals. In the neighborhood of the bone there are numerous areas of hyaline cartilage which have no relation to the bone. In addition to the bundles of nerves in the tumor, single nerve fibres are found in considerable numbers. Very many striated muscular fibres are present. In some places these are collected in well-defined masses with a more or less evident connective-tissue fascia around them. In others they appear as single fibres. The medullary nerve fibres are found in considerable numbers in the masses of muscle. In places aggregations of nuclei, apparently corresponding to muscle plates, are found, but no connection between these and the nerves can be made out. A small amount of adipose tissue is found in the tumor.

In several of the sections the solid portion of the tumor over large areas has the general characteristics of central nervous tissue. In this there is an intercellular reticulum consisting of a loose network of

fibres, which are frequently in connection with the processes of spindle and stellate cells. There are numerous nerve cells in this tissue, both scattered irregularly and in small groups. Many of them are triangular and similar to those of the cerebral cortex. The general aspect of the tissue here is similar to that of cerebral tissue, but no separation into white and grey matter can be made out. In several places there is an almost complete reproduction of the cortex of the cerebellum, the tissue here being characterized by the presence of large branching cells like the cells of Purkinje. The main processes from these cells extend up into the reticular tissue, which contains scattered round cells. On the other side the tissue is closely packed with round cells, but no nerve fibres can be made out in it. On the surface which corresponds to the dura there are numerous round cells and much fibrous tissue. In this part of the tumor there is a cyst, lined with low cuboidal epithelium with numerous papillary ingrowths at various places and numerous secondary cysts. A large number of vessels and a small amount of loose connective tissue are found in these papillary ingrowths. In places the epithelium covering the papillae and that of the cyst are ciliated. This structure corresponds so closely to the choroid plexus that it could easily be demonstrated as being identical with it. The portions of the tumor, which so closely resemble the cerebrum, are generally found adjoining spaces which appear in the specimen more as fissures than as true cysts.

The genuine cysts in the specimen are lined with epithelium of various sorts, and many of them contain masses of desquamated epithelial cells. At various places in the wall of some of the cysts hair bulbs are found, and between these lie numerous sebaceous glands. The adipose tissue spoken of appears in places normal; in other places the oil globules are contained in large spindle cells. There are numerous fissures in the specimen, lined with low, flat endothelium. These apparently correspond to lymphatics. In several places there are large cysts lined with high columnar epithelium and in their walls there are deep depressions, resembling the glands of Lieberkühn, which extend into the tissue. Close beneath the epithelium there is a layer of non-striated muscular tissue, the fibres of which are arranged in

small bundles. Beneath, there is a connective-tissue layer, which contains large numbers of blood-vessels, the appearance of the whole being very similar to that of the submucous tissue of the intestine. Under this is a thick layer of smooth muscular fibres having a definite course, and beneath this again masses of muscular fibres are seen extending in the opposite direction. This area is strongly suggestive of a section of the alimentary canal.

In another part of the specimen there is a very irregular cyst with long projections lined with columnar epithelium extending into the tissue beneath, and in the vicinity are conglomerate glands lined with columnar epithelium. No definite structures which could be regarded as belonging to the sexual system are found, nor are there any which agree in character with the liver, spleen, or kidneys. Lymphatic tissue is abundantly present, both in the form of small cellular aggregations around the vessels and in larger masses which correspond perfectly in their structure to that of lymph glands.

In this case a teratoma of the testicle was present at the birth of the child. It grew rapidly, was removed, and there was no return, the wound healing by first intention. The tumor on microscopic examination contained tissues which could be referred to all three of the germinal layers. A short while after birth a tumor appeared on the head, which was partly removed. It continued to grow rapidly and finally attained a size greater than that of the normal head. On microscopic examination this tumor also was found to contain tissues referable to all of the germinal layers. There is little doubt that the cyst lined with cylindrical epithelium and with definite layers of non-striated muscular fibres on the outside should be regarded as representing intestine. The tumor of the head was especially remarkable for the presence of a large amount of tissue belonging to the central nervous system. Most of this had no very definite arrangement. In places, however, the structure of the cerebellar cortex was definitely shown.

There can be no question that both tumors were of independent origin, and that the tumor of the head could not be regarded as due to metastasis from the testicle. The independent development of the

second growth is shown by the fact that it contained tissues which were not found in the tumor of the testicle. We must regard the metastasis of tumors as due to the conveyance of cells from the primary tumor to some other part of the body, by the blood or lymphatic vessels, where they develop into similar growths. In the case of the teratomata it would be necessary to assume that the metastasis is due to the conveyance, not of cells, but of portions of tissue representing all the complicated structures of the teratoma. Such masses of cells could not be carried through the capillary circulation or the lungs. And even if a metastasis could be supposed to have taken place in fœtal life, such masses of cells and tissue would have lodged either in the placenta or liver.

The general etiology of teratomata is unknown. They represent a variety in which there is a more complex structure than is found in any other class of tumors. The most diverse tissues may be found, and these are frequently arranged in the form of more or less definite organs. Tissues which represent all of the germinal layers of the embryo may be found in them as in the present case.

The theories regarding the formation of tumors may be briefly stated as follows: (1) The influence of a trauma exciting the cells to proliferation. (2) The influence exercised by parasites. (3) Abnormalities of development, in consequence of which certain cells or portions of tissue retain their embryonic character and afterwards develop into tumors. (4) The influence of pathological conditions which may separate certain cells or portions of tissue from their organic connection. The third of these theories, that of Cohnheim, is commonly used to explain the teratomata. It is assumed that in the course of development certain cells not belonging to the part may accidentally become enclosed in the developing organ. These cells retain their specific type and may give rise to new growths which will have the characters of the tissues into which these cells should have developed. It is very probable that the simple teratomata, especially dermoid cysts, may be explained in this way. As regards the internal organs, teratomata are most common in the ovary and the testicle. With our present knowledge of embryology it is impossible to see how

cells belonging to the epiderm or the entoderm could have been enclosed in either the ovary or the testicle, since both these organs develop from cells which are early differentiated from the mesothelium. It is only possible to assume that the tumor of the testicle must have developed from the cells of this gland.

In the case of the teratoma of the head it is difficult to give any explanation. This tumor was outside of the brain and lay between the dura and the skull, neither of which structures took part in its formation. A survey of the literature failed to reveal a similar case. Teratomata within the cranium are not very uncommon. They are found most frequently at the base of the brain in the situation of the pituitary body. They have also been described in the ventricles of the brain. The only instance which we have found in the literature in any way analogous to our case was one described by Aretaeos* and reported before the Royal Medical Society of Athens. The specimen was obtained from Dr. Milliaresis of Cephalonia. This case appeared to be one of twin pregnancy in which one fœtus was an acardiac parasite. The second child was a male of a size corresponding to that of a fœtus at the 7th month. The head was as large as in a case of hydrocephalus and had in the region of the anterior fontanel an opening with ragged torn edges. Through this it is probable that the first embryo had come, because it could be easily thrust through the opening, and there was room for it inside the skull. There was a third very incompletely formed embryo within the meninges. The brain substance was pressed towards the base of the cranium. There was no defect in the brain. The third fœtus seemed to be connected with the medulla oblongata by a pedicle. It represented a more or less uniform mass, but two upper extremities and one lower extremity could be seen. Aretaeos thought, from a closer examination of the third fœtus, that there might have been parts of another fœtus included in this. The whole description of the case is very imperfect and it is difficult to make out the exact relation of the various fœtuses and the portions of them.

It is possible to suppose that there may have been in our case a

* Virchow's *Archiv*, xxiii, p. 428, 1862.

double germinal area, one area developing into a fœtus which included within its skull the other undeveloped germ. The cases of double monstrosity in which the two embryos are united head to head are usually explained by the supposed presence of two germinal areas in the ovum arranged in such a way that the two cephalic extremities come in contact in the process of growth. It is possible that one of these may not develop and in the course of growth may become included within the cranium of the fœtus. This explanation would apply much more easily to those teratomata which are found within the ventricles of the brain, because in that situation they could have been enclosed in the medullary groove. In our case the tumor lay entirely without the medullary groove, and the embryonic tissue must have been enclosed not in the medullary canal, but within the lateral plates. We could not regard such a structure as due to fission with inclusion of the separated portion, after the differentiation of the embryo had taken place to any degree. It is not impossible that it may have arisen from fission at a very early cell stage, the separated portion becoming included, and afterwards going on to the development of a tumor.

Recent experiments in embryology have shown that on separation of the cells of the blastoderm, the cell or cells so separated may develop either into perfect embryos or, retaining a partial connection, form double monsters. There is no case known in which separated cells of the blastoderm remain enclosed in other masses of cells and afterwards undergo development. We could not explain why the teratomata formed from such cells should develop by preference in certain situations. Although these experiments have thrown much light on the formation of double monsters, they have not given us any explanation of the teratomata. The great number of tissues found in this case could only be explained by the supposition that either an entire germinal area was included or cells from a very early stage of segmentation.

The points of surgical interest in the case are: (1) The very close way in which the original tumor simulated a congenital hydrocele, even to the extent of twice yielding a certain amount of straw-colored fluid. (2) The complete recovery from the first operation. (3) The

fact that complete removal of the tumor of the head was probably possible at the time when it was first noticed, could a diagnosis of its exact situation have been made. But the diagnosis presented insuperable difficulties, for a tumor apparently of malignant nature had been removed from the scrotum and was followed some months later by a tumor presenting clinical aspects of malignancy, which was naturally attributed to metastasis. (4) That such extensive pressure of the motor area of the brain could exist without any trace of motor symptoms.

DESCRIPTION OF PLATE XXXV.

Fig. 1.—Head of child from a photograph taken during life.

Fig. 2.—Section through the tumor of the head; about two-thirds of the natural size.

FIG. 1.

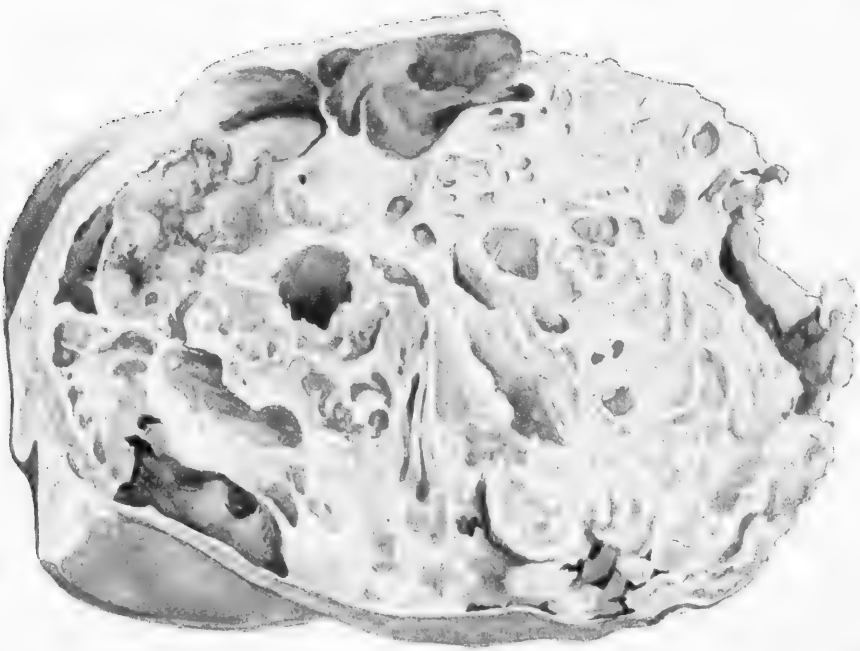

FIG. 2.

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α-METHYL-QUINOLINE AS A CONSTITUENT OF THE SECRETION OF THE ANAL GLANDS OF MEPHITIS MEPHITICA.

By THOMAS B. ALDRICH, Ph. D.,

AND

WALTER JONES, Ph. D.

(*From the Laboratory of Physiological Chemistry of the Johns Hopkins University.*)

In 1863 Swarts* (in Wöhler's laboratory) noticed in the secretion of the anal glands of M. mephitica the presence of a basic body which from its volatility and odor he referred to methyl- or ethyl-amine. Later, in 1879, Loew† stated that the secretion contains a basic body which smells like trimethylamine, and no doubt has a constitution similar to that of neurin. Up to the present time, beyond these conjectures, nothing has been done to characterize or to establish the identity of this body.

As has been stated in a previous communication,‡ the secretion can be readily separated, by distillation, into two sharply defined, nearly equal portions:

1. A more volatile portion, boiling between 100°–130° C., and which for convenience we have designated A.

2. A less volatile portion, left after distilling off A, and which has been called B.

A is a colorless liquid having a neutral reaction, and is further characterized by an unpleasant penetrating odor and by the readiness with which it reacts with mercuric oxide, mercuric cyanide and lead acetate, forming with these reagents for the most part crystalline compounds. It is a mixture of the higher mercaptans, containing among others (still undetermined) normal butyl mercaptan.§

* Liebig's *Annalen*, cxxvii (1862), 266.

† *Aerztliches Intelligenzblatt*, München, June 10, 1879, 252.

‡ T. B. Aldrich, *Journal of Experimental Medicine*, i, 323, 1896.

§ *Journal of Experimental Medicine*, i, 332–336.

The oil B has a dark red color, a neutral reaction, and a less penetrating odor than A. It contains carbon, hydrogen, nitrogen and sulphur, and does not react with the reagents mentioned under A, thus excluding the presence of mercaptans, at least to any considerable extent.

By careful and not too rapid distillation it is possible to separate the mercaptans from B completely,* though to insure a perfect separation it is advisable to shake B with a 50 per cent solution of potassium hydroxide, which not only removes the mercaptans, but also other bodies of acid nature. Accordingly, a small quantity of ether was added to B, and this ethereal solution agitated three successive times with an excess of a 50 per cent potassium hydroxide solution, the alkaline solution removed each time, and finally the ethereal solution washed with successive portions of distilled water until the alkaline reaction disappeared. The resulting oil after this treatment is free from mercaptans and bodies of acid nature, and contains neutral and basic bodies either originally in the secretion or split off by the strong alkali. B after being treated in this manner is a clear fluid, possessing a reddish yellow color; it constituted in one instance 42 per cent of the original secretion; it still contains C, H, N, and S.

It has been stated in a previous communication by one of us† that B contains a basic body either free or combined with some other constituent of the secretion; at that time a small amount of the impure base was isolated and platinic and gold chloride compounds were made.

BASIC BODY ISOLATED FROM B.‡

For the purpose of extracting the basic body from B the latter was shaken three times in succession with an equal volume of a 5 per cent hydrochloric acid solution (ether being added to facilitate the separation) and each acid extract washed once with an excess of ether. By

* This is especially true when working with small quantities.

† T. B. Aldrich, op. cit.

‡ B freed of the basic body is a clear, yellowish red, oily looking liquid, having a peculiar sweetish nauseating smell, and constituting about 37 per cent of the original secretion. For convenience we will call it B_1. It contains about 25 per cent of sulphur. We hope in the near future to state something more definite in regard to this portion of the secretion.

evaporating separately each acid extract* so treated it was found that the first contained approximately all of the basic substance, and that it deposited nearly colorless, transparent, needle-like crystals, evidently the hydrochloride of the basic substance, when evaporated nearly to dryness on the water-bath or when placed in a desiccator over sulphuric acid.

In order to obtain the free base the hydrochloric acid compound was decomposed with sodium hydroxide and the liberated base distilled with steam. By this process an oil was obtained having a light greenish color and a peculiar odor very similar to that of quinoline and its homologues. The water which dissolved the base slightly had a faint alkaline reaction, and fumes were observed when dilute hydrochloric acid was held near the vessel containing the distillate. By this procedure, however, it became evident that we had extracted at least two bodies with the acid solution, one readily volatile with steam and passing over in the first 200 or 300 cc. of the distillate, the other very much less, though still partially, volatile. If the distillation is continued too long the former body becomes mixed with the less volatile and loses to a certain extent its characteristic odor. In order to obtain the former approximately pure the distillation was usually discontinued as soon as the distillate after acidification with hydrochloric acid ceased to give with gold chloride a crystalline precipitate.

Boiling with an excess of pure silver oxide suspended in water decomposes the hydrochloride salt of the base very incompletely. Indeed, after boiling an hour the greater part of the compound was found to be undecomposed, for when sodium hydroxide was added an oil was liberated which was readily carried over with steam and which gave the characteristic odor etc. of the base.

It may be stated in passing that the less volatile body differs from the more volatile in containing sulphur. Whether or not this substance is a mixture of a basic body with some of the portion called B_1 has not been determined. It dissolves, though neither readily nor completely, in dilute hydrochloric acid, and this solution gives with

* The second and third acid extracts left, on evaporation, a reddish oil, possessing properties different from those of the residue of the first.

platinic and gold chloride amorphous yellow precipitates. It seems probable that in shaking B with acid some of B_1 was taken up by the acid; this would explain the presence of sulphur in this body.

The impure basic body after distillation with steam was collected with ether; it constituted about 5 per cent of the original secretion. Further purification can be accomplished by passing the oil through one of its numerous salts. The zinc chloride double salt was used, although others may be employed with equally good results.

PURIFICATION OF THE BASE BY MEANS OF THE ZINC CHLORIDE DOUBLE SALT.

The base was dissolved in dilute hydrochloric acid and an aqueous solution of zinc chloride added as long as a precipitate was formed. The precipitate was recrystallized from dilute hydrochloric acid, then decomposed with sodium hydroxide, after which the free base was distilled with steam and collected with ether.

Prepared in this manner the base is colorless, has the quinoline odor, and is highly refractive. It is soluble in ether, alcohol, chloroform and acids; slightly soluble in both cold and hot water; insoluble in alkalies. It forms salts with the mineral as well as with the organic acids. The salts of the mineral acids are, as far as investigated, easily soluble in water, or in the respective acid used, and may be obtained in crystalline form by evaporating on the water-bath nearly to dryness, or allowing their solutions to evaporate in a desiccator. The majority of them may be recrystallized from hot alcohol. The hydrochloride salt forms needles, soluble in water and alcohol, insoluble in ether.

The base also forms double salts with platinic and gold chloride, zinc chloride etc., most of which can be obtained in crystalline form.

Among the derivatives which the base forms may be mentioned a bromine and a methyliodide compound. The base also responds to most of the alkaloidal reagents.

The small quantity of the impure base, not over four or five grammes, which we were able to obtain, necessitated the preparation and analysis of some of the most characteristic salts and derivatives rather than the base itself.

The following pages contain an account of the preparation, properties and analyses of a few of the most characteristic salts and derivatives; we wish to say that while some of these compounds were obtained from the pure base, others were made from the impure product before passing it through the zinc chloride salt.

Platinum Chloride Double Salt ($[C_{10}H_9N.HCl]_2PtCl_4$).

This salt, one of the most characteristic, is deposited in the form of yellow needles when platinic chloride is added to a dilute hydrochloric acid solution of the base. It is obtained as orange-red needles when recrystallized from water or dilute hydrochloric acid. Dried in the air or *in vacuo* over sulphuric acid the salt does not contain water of crystallization, melts under decomposition between 226°–230° C., and gave on analysis the following results:

I. 0.2479 gramme substance gave 0.3155 gramme CO_2, and 0.0651 gramme H_2O.
II. 0.2422 " " " 0.3059 " " and 0.0642 " "
I. 0.1586 " " " 0.0446 " Pt.
II. 0.1827 " " " 0.0514 " "
I. 0.1764 " " " 0.2175 " AgCl.
II. 0.0643 " " " 0.0790 " "
I. 0.1971 gr. substance gave 6.1 cc. moist N at 24° C. under a pressure of 764 mm.
II. 0.1977 " " 6.8 " " 22° " " "

	Calculated for $[C_{10}H_9NHCl]_2PtCl_4$.	Found. I.	Found. II.
C	34.53	34.71	34.44
H	2.88	2.92	2.94
N	4.02	3.94	3.92
Pt	27.93	28.12	28.13
Cl	30.64	31.14	30.47

The platinum compound is further characterized by being very sparely soluble in cold water, and by giving rise, when decomposed by heating in a dry test tube, to a volatile oil which on cooling deposits transparent colorless needles. These needles are soluble in water, alcohol and dilute hydrochloric acid, insoluble in ether, and are no doubt the hydrochloride salt of the base, the solubilities of which agree with these. The volatility of the base with hydrochloric acid also explains the difficulty experienced in testing qualitatively for nitrogen in this compound. The melting point given above agrees exactly with that of a platinum compound obtained by Fischer and Kuzel* from a basic body which from

* *Ber. d. deutsch. chem., Gesellsch.*, xvi, 165.

analyses they claim to have proved to be identical with Döbner and von Miller's* α-methyl-quinoline.

Gold Chloride Double Salt ($C_{10}H_9N$. HCl Au Cl_3).

When an aqueous solution of gold chloride is added to a hydrochloric acid solution of the base a turbidity is produced, giving place in a few minutes to a network of fine slender yellow needles. When recrystallized from dilute hydrochloric acid or water the salt is deposited in the form of glistening yellow needles. Dried *in vacuo* over sulphuric acid the compound melts sharp at 153° C. and gives the following analytical results:

I. 0.2036 gramme substance gave 0.1848 gramme CO_2, and 0.0409 gramme H_2O.
II. 0.2991 " " " 0.2672 " " and 0.0580 " "
I. 0.1261 " " " 0.0511 " Au.
II. 0.2013 " " " 0.0819 " "
I. 0.1155 " " " 0.1359 " AgCl.
II. 0.0848 " " " 0.0999 " "
I. 0.1939 gr. substance gave 4.9 cc. moist N at 22° C. under a pressure of 764 mm.
II. 0.2023 " " " " " " " " " "

	Calculated for $C_{10}H_9N.HClAuCl_3$.	Found. I.	Found. II.
C	24.87	24.75	24.37
H	2.09	2.23	2.16
N	2.90	2.82	2.76
Au	40.72	40.52	40.68
Cl	29.42	29.18	29.22

The gold chloride compound is characterized by its greater solubility, in both cold and hot dilute hydrochloric acid, than the corresponding platinum compound. It also, on heating in a dry test tube, gives off a volatile body which is deposited in the form of crystals in the cold part of the tube, though this property is not so pronounced as in the case of the platinum compound.

Bichromate Salt $[(C_{10}H_9N)_2 . Cr_2O_7H_2]$.

Among the salts of quinoline and its homologues none are more characteristic than those of the bichromates. This compound of the base is precipitated as a yellow-red oil, crystallizing almost immediately when an aqueous solution of potassium bichromate is added to the hydrochloric acid solution of the base. It crystallizes from hot water in the form of yellow-red needles, which in their color and crystalline form are hardly to be distinguished from the platinum double salt. Dried in a desiccator

* *Ber. d. deutsch. chem. Gesellsch.*, xv, 3075.

it melts under decomposition at 130°–140° C. When heated rapidly, like the corresponding salt of quinoline, it decomposes suddenly. It is with difficulty soluble in cold, readily in hot water.

Incineration of the salt gave the following result:

0.1694 gramme substance gave 0.0508 gramme Cr_2O_3.

	Calculated for $[C_{10}H_9N]_2.Cr_2O_7H_2$.	Found.
Cr	20.76	20.58

Picrate Salt $[C_{10}H_9N \cdot C_6H_2(NO_2)_3 \cdot OH]$.

The picrate is precipitated as an insoluble yellow cloud, changing almost immediately into yellow crystals whenever a saturated aqueous solution of picric acid is added to a hydrochloric acid solution of the base. Recrystallized from a saturated alcoholic solution it is deposited as glittering yellow needles; from a dilute solution it forms well-defined prisms. Dried *in vacuo* over sulphuric acid it melts when heated rapidly at 177° C.; when heated gradually it melts between 193° and 194° C.

A nitrogen determination gave the following results:

I. 0.1953 gramme substance gave 25.6 cc. moist N at 22° C. under a pressure of 764.5 mm.

II. 0.1957 gramme substance gave 26 cc. moist N at 20° C. under a pressure of 764.5 mm.

	Calculated for $C_{10}H_9N.C_6H_2(NO_2)_3OH$.	Found.	
		I.	II.
N	15.05	14.93	15.27

This salt is sparingly soluble in cold water or alcohol, readily soluble in hot alcohol.

Owing to the very limited amount of material at our disposal the following salts and derivatives were not obtained in sufficient quantity for analysis.

Zinc Chloride Double Salt $[(C_{10}H_9N \cdot H\,Cl)_2 \cdot Zn\,Cl_2]$.

As has already been stated, under purification of the base, this salt is formed when an aqueous solution of zinc chloride is added to the hydrochloric acid solution of the base. It is of especial importance from the fact that it is suitable for the purification of the base, being readily soluble in hot water, quite insoluble in cold. From its hot alcoholic and from its dilute aqueous solution it crystallizes in transparent colorless monoclinic crystals which in general appearance might be mistaken for gypsum crystals, although twin crystals have not been observed. It is insoluble in ether, sparingly soluble in cold alcohol and water, readily soluble in hot alcohol, water and dilute acids. Recrystallized from

water and dried in the air the salt melts under decomposition between 230°–240° C.

Hydroferrocyanic Acid Salt $[(C_{10}H_9N)_2 . H_4Fe(CN)_6]$.

This salt is formed whenever an aqueous solution of potassium ferrocyanide is added to the acid solution of the base. It can be readily obtained in the form of transparent prisms from hot dilute acids. It is decomposed readily by alkalies, and may thus be used to advantage in purifying the base.

Silver Nitrate Salt $[(C_{10}H_9N)_2AgNO_3]$.

This salt is obtained when an aqueous solution of silver nitrate is added to an alcoholic solution of the base. It is obtained from alcohol in transparent colorless needles.

Methyl Iodide Addition Product $[C_{10}H_9N . CH_3I]$.

If equal parts by weight of methyl iodide and the base are brought together and warmed gently on the water-bath (using a reflex condenser) reaction takes place, and yellow needle-shaped crystals are soon deposited. This compound is very soluble in alcohol and water, insoluble in ether; and though characteristic in appearance, has nevertheless been difficult to obtain.

Bromine Addition Product.

This compound is most conveniently prepared in a chloroform solution. The base was dissolved in chloroform and a corresponding solution of bromine added until the color persisted. Upon the addition of ether a crystalline compound was precipitated which, when filtered and washed with ether, became nearly colorless. The body is obtained as beautiful colorless prisms when recrystallized from alcohol containing ether, or when dissolved in chloroform and precipitated with ether. The compound may also be prepared in glacial acetic acid solution and precipitated with water. It is readily soluble in hot alcohol, also in chloroform and glacial acetic acid; insoluble in ether and water.

Quinaldine Yellow $[C_{10}H_9N . (CO_2)C_6H_4]$.*

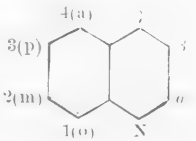
Equivalent weights of the base, phthalic anhydride and anhydrous zinc chloride were heated together in a bath at 200° C. from three to four hours. The resulting product was dissolved in concentrated sulphuric acid at water-bath temperature and then poured into twenty times its volume of water, with the result that a reddish brown flocculent body was

* *Ber. d. deutsch. chem. Gesellsch.*, xvi, 1602.

precipitated. Filtered and recrystallized, first from glacial acetic acid and then twice from hot 98 per cent alcohol, beautiful, fine, lustrous yellow needles were obtained. Dried in the air the body melts without decomposition between 235°–240° C. to a cherry-red liquid. The compound is very soluble in glacial acetic acid, readily in hot alcohol and concentrated sulphuric acid; insoluble in water, ether and dilute acids; sparingly soluble in cold alcohol.

The analytical data given on the preceding pages agree with those of a base having the empirical formula $C_{10}H_9N$. This body is therefore identical or isomeric with the naphthylamines ($C_{10}H_7NH_2$) or the methyl-quinolines ($C_9H_6CH_3N$). Since, however, the former are solids at ordinary temperatures, the base can be referred only to the latter. Indeed, the whole deportment of the base—odor, similarity of salts etc.—stamps it as a quinoline homologue.

Of the seven normal monomethyl-quinolines in which the methyl group occupies either the α, β, γ, 1(o), 2(m), 3(p), or 4(a), position in the following structural formula,



the base agrees perfectly, as far as investigated, with the α-compound.

The following considerations lead to this conclusion:

1. The platinum double salt of the base contains no water of crystallization; all of the platinum double salts of the seven normal monomethyl-quinolines, with the exception of the α-compound, contain one or two molecules of water of crystallization.*

2. The platinum double salt of the base melts, similarly to that of α-methyl-quinoline, between 226°–230° C.† under decomposition.

3. The crystalline form, color, solubilities and melting points of the

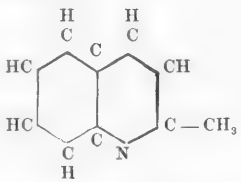
* Of the seven possible isomethyl-quinolines, only three, as far as the literature is known to us, have been prepared. The platinum compounds of two of these contain water of crystallization; the platinum salt of the third melts at 253.5° C. These bases are therefore not identical with the basic body in the secretion. The normal anamethyl-quinoline is excluded through its picrate with m. pt. 208°–209° C.

† E. Fischer u. Kuzel, *Ber. d. deutsch. chem. Gesellsch.*, xvi, 165.

other salts and derivatives of the base, as far as prepared, agree very closely, and in most instances exactly, with those of α-methyl-quinoline.

4. Quinoline yellow,* formed by the action of phthalic anhydride and zinc chloride on α-methyl-quinoline, deports itself precisely like the corresponding compound of the base.

These points of resemblance, when considered together with the properties of the base itself (odor, volatility, solubilities etc.), would seem to afford evidence sufficient to warrant the assertion that the base is identical with α-methyl-quinoline, and consequently has the well known structural formula,



For purposes of comparison α-methyl-quinoline was prepared synthetically,† and its salts and derivatives compared with those of the base.

Synthetic Preparation of α-Methyl-quinoline.

The base was prepared by heating together for four or five hours on the water-bath a mixture of 1½ parts of paraldehyde, 2 parts of concentrated hydrochloric acid, and 1 part of aniline.

The best result was obtained by making the hydrochloride of aniline first and then adding the paraldehyde in small portions, avoiding excessive heating, and finally finishing on the water-bath. At the end of this time a current of steam was passed through the mixture, thus removing a small quantity of oil. The whole mass was then made strongly alkaline, the receiver changed and the distillation continued. A light green oil passed over, which was collected with ether. The base was freed of aniline by dissolving the oil in dilute hydrochloric acid and adding an excess of an aqueous solution of zinc chloride. The crystalline precipitate was recrystallized once from dilute hydrochloric acid and treated as heretofore explained for the purification of the base. Since aniline does not form an insoluble zinc salt it is possible in this manner to separate the two bases.

* *Ber. d. deutsch. chem. Gesellsch.*, xvi, 2602.
† Döbner u. von Miller, op. cit., xvi, 2465.

The base so prepared is colorless, highly refractive, possesses the quinoline odor, and boils between 230°–240° C.

In the following table some of the derivatives of the basic body from the secretion and those of *α*-methyl-quinoline are compared.

*α-Methyl-Quinoline (from M. mephitica). B. Pt. ——.**

When pure the base is a highly refractive, colorless oil, having a faint quinoline odor (very pronounced on warming). It is readily volatile with steam, gives fumes when hydrochloric acid is held near it, is readily soluble in ether, chloroform, alcohol and mineral acids; insoluble in alkalies, sparingly soluble in both hot and cold water.

SALTS AND DERIVATIVES.

	Soluble in	Insoluble in	M. Pt.	Form.	Color.	Water of crystallization.
Platinum.	H_2O, dil. HCl, alcohol.	ether.	226°–230° C. (decomposition).	cryst. (needles).	orange-red.	none.
Gold.	H_2O, dil. HCl, alcohol.	ether.	153° C. (decomposition).	cryst. (needles).	yellow.	none.
Picrate.	hot alcohol.	H_2O, ether.	193°–194° C. (decomposition).	cryst. (needles or prisms).	yellow.	none.
Bichromate.	hot H_2O.	cold H_2O, ether.	130°–140° C. (decomposition).	cryst. (needles).	orange-red.	none.
Quinaldine yellow.	glac. acetic acid, hot alcohol, con. H_2SO_4.	H_2O, ether, dil. acids.	235°–240° C. (red liq'd, solidifies).	cryst. (needles).	golden yellow.	——
Zinc.	hot H_2O, hot alcohol, " dil. acids.	ether, sparingly sol. in alcohol & cold H_2O.	230°–240° C. (decomposition).	cryst. (monoclinic).	colorless.	——
Methyl iodide.	H_2O, alcohol.	ether.	——	cryst. (needles)	yellow.	——
Bromine.	chloroform, glac. acetic acid, hot alcohol.	ether, H_2O.	——	cryst. (prisms).	colorless.	——

* The small quantity of the base prevented the determination of the b. pt.

α-Methyl-quinoline (Synthetic). B. Pt. 235°–240° C.*

When pure α-methyl-quinoline is a highly refractive, colorless oil, having a faint quinoline odor, very pronounced on warming. It is readily volatile with steam, gives fumes when hydrochloric acid is held near it, is readily soluble in ether, chloroform, alcohol and mineral acids; insoluble in alkalies, sparingly soluble in both hot and cold water.

SALTS AND DERIVATIVES.

	Soluble in	Insoluble in	M. Pt.	Form.	Color.	Water of crystallization.
Platinum.	H_2O, dil. HCl, alcohol.	ether.	226°–230° C. (decomposition).	cryst. (needles).	orange-red.	none.
Gold.	H_2O, dil. HCl, alcohol.	ether.	153° C. (decomposition).	cryst. (needles).	yellow.	none.
Picrate.	hot alcohol.	H_2O, ether.	193°–194° C. (decomposition).	cryst. (needles or prisms).	yellow.	none.
Bichromate.	hot H_2O.	cold H_2O, ether.	130°–140° C. (decomposition).	cryst. (needles).	orange-red.	none.
Quinaldine yellow.	glac. acetic acid, hot alcohol, con. H_2SO_4.	ether, dil. acids, H_2O.	235° C. (red liq'd, solidifies).	cryst. (needles).	golden yellow.	——
Zinc.	hot alcohol, " water. " dil. acids.	ether, sparingly sol. in cold H_2O & alcohol.	230°–240° C. (decomposition).	cryst. (monoclinic).	colorless.	——
Methyl iodide.	H_2O, alcohol.	ether.	195° C.	cryst. (needles).	yellow.	——
Bromine.	glac. acetic acid, chloroform, hot alcohol.	ether, H_2O.	——	cryst. (prisms).	colorless.	——

* Döbner u. von Miller (op. cit., xvi, 2464) gave 238°–239° C. Others give from 240°–247° C.

The presence of α-methyl-quinoline in the animal organism deserves more than passing notice. This is the first time its natural occurrence has been demonstrated either in the vegetable or animal kingdom. It is true that a few of the methyl-quinolines, together with related bases, have been found among the products resulting from the destructive distillation of nitrogenous organic matter, but up to the present time they have never been demonstrated as products other than of laboratory methods. Thus Jacobsen and Reimer* found α-methyl-quinoline in coal-tar, while Williams† obtained γ-methyl-quinoline (lepidine) by distilling cinchonine with potash. Furthermore, it is to be observed that quinoline and its homologues are confined, for the most part, to the vegetable world.

When we consider the number of nitrogenous organic bodies that are found in the tissues and fluids of the body, or when we consider the diversity of the products formed through the activity of the living cells, it does not seem strange that α-methyl-quinoline should be found among these products. Indeed, the isolation of kynurenic acid (oxy-quinolin-carboxylic acid) from the dog's urine, first by Liebig,‡ and later by different methods by Hoffmeister,§ Brieger,‖ Schmiedeberg and Schultzen,¶ proved the presence of quinoline in the animal organism. There is no doubt but that these quinoline compounds have their origin in the proteid molecule, for, according to Baumann,** the amount of kynurenic acid in the urine under ordinary conditions is dependent upon the nature of the food supplied to the animal, being greatest under a proteid diet. It is interesting to note also in this connection that the food of the skunk consists exclusively of proteid matter.

The indications are that α-methyl-quinoline is free, that is, not combined with any other substance in the secretion, for it can be partially extracted from B, or the original secretion, by shaking persist-

* *Ber. d. deutsch. chem. Gesellsch.*, xvi, 1082.
† *Jahresber. f. Chem.*, 1855, 550.
‡ Liebig's *Annalen*, lxxxvi (1853), 125; cviii (1858), 354.
§ *Zeit. f. Phys. Chem.*, v, 67.
‖ *Zeit. f. Phys. Chem.*, iv, 89.
¶ Liebig's *Annalen*, clxiv (1872), 155.
** *Zeit. f. Phys. Chem.*, x (1886), 131.

ently with an excess of water. Furthermore, the compounds thus far isolated from the secretion do not, so far as is known, combine with α-methyl-quinoline.

The fact that α-methyl-quinoline is destroyed when injected subcutaneously* into dogs, supports the view that the cells of the anal glands are directly concerned in the elaboration of this compound. This presumption is furthermore substantiated by the fact that the base has never been found in the blood or in any other tissue of the animal body. We can safely assume that these particular cells, and no others, are concerned in the elaboration of this compound.

In conclusion, we desire to express our thanks to Dr. C. Hart Merriam, Chief of Division of Ornithology and Mammalogy, Washington, D. C., who has kindly furnished us with part of the material used in this investigation.

* R. Cohn, *Zeit. f. Phys. Chem.*, xx, 210.